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Request for grant of a patent

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1. Your reference PA 552

2. Patent application number *(The Patent Office will fill in this part)* 0324902.6

24 OCT 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CELLTECH R&D LIMITED
208 BATH ROAD
SLOUGH, SL1 3WE
BERKSHIRE
GB

Patents ADP number *(if you know it)* 8121485001

If the applicant is a corporate body, give the country/state of its incorporation ENGLAND AND WALES

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent *(if you have one)* DR. JOHN THOMPSON, CPA, EPA

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

CELLTECH R&D LIMITED
208 BATH ROAD
SLOUGH, SL1 3WE
BERKSHIRE

Patents ADP number *(if you know it)* 8121485002

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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b) there is an inventor who is not named as an applicant, or
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Request for preliminary examination and search *(Patents Form 9/77)*	
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11. I/We request the grant of a patent on the basis of this application.

Signature J Thompson Date 23.10.03

12. Name and daytime telephone number of person to contact in the United Kingdom DR. JOHN THOMPSON - 01753 534655

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THERAPEUTIC AGENTS

This invention relates to a series of substituted thieno[2,3-*b*]pyridin-6(7*H*)-one derivatives, to compositions containing them, to processes for their preparation and to their use in medicine.

Immune and inflammatory responses involve a variety of cell types with control and co-ordination of the various interactions occurring *via* both cell-cell contacts (e.g. integrin interactions with their receptors) and by way of intercellular signalling molecules. A large number of different signalling molecules are involved including cytokines, lymphocytes, chemokines and growth factors.

Cells respond to such intercellular signalling molecules by means of intracellular signalling mechanisms that include protein kinases, phosphatases and phospholipases. There are five classes of protein kinase of which the major ones are the tyrosine kinases and the serine/threonine kinases [Hunter, T., *Methods in Enzymology (Protein Kinase Classification)*, p. 3, Hunter, T. and Sefton, B.M. eds., vol. 200, Academic Press, San Diego, 1991].

One sub-class of serine/threonine kinases is the mitogen activating protein (MAP) kinases of which there are at least three families which differ in the sequence and size of the activation loop [Adams, J. L. *et al.*, *Progress in Medicinal Chemistry*, pp. 1-60, King, F.D. and Oxford, A.W. eds., vol. 38, Elsevier Science, 2001]: the extracellular regulated kinases (ERKs); the c-Jun NH_2 terminal kinases or stress activated kinases (JNKs or SAP kinases); and the p38 kinases, which have a threonine-glycine-tyrosine (TGY) activation motif. Both the JNKs and p38 MAP kinases are primarily activated by stress stimuli including, but not limited to, proinflammatory cytokines, e.g. tumour necrosis factor (TNF) and interleukin-1 (IL-1), ultraviolet light, endotoxin and chemical or osmotic shock.

Four isoforms of p38 have been described (p38α/β/γ/δ). The human p38α enzyme was initially identified as a target of cytokine-suppressive anti-inflammatory drugs (CSAIDs) and the two isoenzymes found were initially termed CSAID binding protein-1 and -2 (CSBP-1 and CSBP-2 respectively) [Lee, J. C. *et al.*, *Nature (London)*, 1994, **372**, 739-46]. CSBP-2 is now widely referred to as p38α and differs from CSBP-1 in an internal sequence of 25 amino acids as a result of differential splicing of two exons

that are conserved in both mouse and human [McDonnell, P.C. *et al.*, *Genomics*, 1995, **29**, 301-2]. CSBP-1 and p38α are expressed ubiquitously and there is no difference between the two isoforms with respect to tissue distribution, activation profile, substrate preference or CSAID binding. A second isoform is p38β which has 70% identity with p38α. A second form of p38β termed p38β2 is also known and of the two this is believed to be the major form. p38α and p38β2 are expressed in many different tissues. However, in monocytes and macrophages p38α is the predominant kinase activity [Lee, J.C., *ibid*; Jing, Y. *et al.*, *J. Biol. Chem.*, 1996, **271**, 10531-34; Hale, K.K. *et al.*, *J. Immun.*, 1999, **162**, 4246-52]. p38γ and p38δ (also termed SAP kinase-3 and SAP kinase-4 respectively) have ~63% and ~61% homology to p38α respectively. p38γ is predominantly expressed in skeletal muscle whilst p38δ is found in testes, pancreas, prostate, small intestine and in certain endocrine tissues.

All p38 homologues and splice variants contain a 12 amino acid activation loop that includes a Thr-Gly-Tyr motif. Dual phosphorylation of both Thr-180 and Tyr-182 in the TGY motif by a dual specificity upstream kinase is essential for the activation of p38 and results in a >1000-fold increase in specific activity of these enzymes [Doza, Y.N. *et al.*, *FEBS Lett.*, 1995, **364**, 7095-8012]. This dual phosphorylation is effected by MKK6 and, under certain conditions, the related enzyme MKK3 [Enslen, H. *et al.*, *J. Biol. Chem.*, 1998, **273**, 1741-48]. MKK3 and MKK6 belong to a family of enzymes termed MAPKK (mitogen activating protein kinase kinase) which are in turn activated by MAPKKK (mitogen activating kinase kinase kinase) otherwise known as MAP3K.

Several MAP3Ks have been identified that are activated by a wide variety of stimuli including environmental stress, inflammatory cytokines and other factors. MEKK4/MTK1 (MAP or ERK kinase kinase/MAP three kinase-1), ASK1 (apoptosis stimulated kinase) and TAK1 (TGF-β-activated kinase) are some of the enzymes identified as upstream activators of MAPKKs. MEKK4/MTK1 is thought to be activated by several GADD-45-like genes that are induced in response to environmental stimuli and which eventually lead to p38 activation [Takekawa, M. and Saito, H., *Cell*, 1998, **95**, 521-30]. TAK1 has been shown to activate MKK6 in response to transforming growth factor-β (TGF-β). TNF-stimulated activation of p38 is believed to be mediated by the recruitment of TRAF2 (TNF receptor associated factor) and the Fas adaptor protein, Daxx, which results in the activation of ASK1 and subsequently p38.

Several substrates of p38 have been identified including other kinases [e.g. MAPK activated protein kinase 2/3/5 (MAPKAP 2/3/5), p38 regulated/activated protein kinase (PRAK), MAP kinase-interacting kinase 1/2 (MNK1/2), mitogen- and stress-activated protein kinase 1 (MSK1/RLPK) and ribosomal S6 kinase-B (RSK-B)], transcription factors [e.g. activating transcription factor 2/6 (ATF2/6), monocyte-enhancer factor-2A/C (MEF2A/C), C/EBP homologous protein (CHOP), Elk1 and Sap-1a1] and other substrates [e.g. cPLA2, p47phox].

MAPKAP K2 is activated by p38 in response to environmental stress. Mice engineered to lack MAPKAP K2 do not produce TNF in response to lipopolysaccharide (LPS). Production of several other cytokines such as IL-1, IL-6, IFN-g and IL-10 is also partially inhibited [Kotlyarov, A. *et al.*, *Nature Cell Biol.*, 1999, **1**, 94-7]. Further, MAPKAP K2 from embryonic stem cells from p38α null mice was not activated in response to stress and these cells did not produce IL-6 in response to IL-1 [Allen, M. *et al.*, *J. Exp. Med.*, 2000, **191**, 859-69]. These results indicate that MAPKAP K2 is not only essential for TNF and IL-1 production but also for signalling induced by cytokines. In addition, MAPKAP K2/3 phosphorylate and thus regulate heat shock proteins HSP 25 and HSP 27 which are involved in cytoskeletal reorganization.

Several small molecule inhibitors of p38 have been reported which inhibit IL-1 and TNF synthesis in human monocytes at concentrations in the low μM range [Lee, J.C. *et al.*, *Int. J. Immunopharm.*, 1988, **10**, 835] and exhibit activity in animal models which are refractory to cyclooxygenase inhibitors [Lee, J.C. *et al.*, *Annals N.Y. Acad. Sci.*, 1993, **696**, 149]. In addition, these small molecule inhibitors are known to decrease the synthesis of a wide variety of pro-inflammatory proteins including IL-6, IL-8, granulocyte/macrophage colony-stimulating factor (GM-CSF) and cyclooxygenase-2 (COX-2). TNF-induced phosphorylation and activation of cytosolic PLA2, TNF-induced expression of VCAM-1 on endothelial cells and IL-1 stimulated synthesis of collagenase and stromelysin are also inhibited by such small molecule inhibitors of p38 [Cohen, P., *Trends Cell Biol.*, 1997, **7**, 353-61].

A variety of cells including monocytes and macrophages produce TNF and IL-1. Excessive or unregulated TNF production is implicated in a number of disease states including Crohn's disease, ulcerative colitis, pyresis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, toxic shock syndrome, endotoxic shock, sepsis, septic shock, gram negative sepsis, bone resorption

diseases, reperfusion injury, graft vs. host reaction, allograft rejection, adult respiratory distress syndrome, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, cerebral malaria, scar tissue formation, keloid formation, fever and myalgias due to infection, such as influenza, cachexia secondary to acquired immune deficiency syndrome (AIDS), cachexia secondary to infection or malignancy, AIDS or AIDS related complex.

Excessive or unregulated IL-1 production has been implicated in rheumatoid arthritis, osteoarthritis, traumatic arthritis, rubella arthritis, acute synovitis, psoriatic arthritis, cachexia, Reiter's syndrome, endotoxemia, toxic shock syndrome, tuberculosis, atherosclerosis, muscle degeneration, and other acute or chronic inflammatory diseases such as the inflammatory reaction induced by endotoxin or inflammatory bowel disease. In addition, IL-1 has been linked to diabetes and pancreatic β cells [Dinarello, C.A., *J. Clinical Immunology*, 1985, 5, 287-97].

IL-8 is a chemotactic factor produced by various cell types including endothelial cells, mononuclear cells, fibroblasts and keratinocytes. IL-1, TNF and LPS all induce the production of IL-8 by endothelial cells. *In vitro* IL-8 has been shown to have a number of functions including being a chemoattractant for neutrophils, T-lymphocytes and basophils. IL-8 has also been shown to increase the surface expression of Mac-1 (CD11b/CD18) on neutrophils without *de novo* protein synthesis, which may contribute to increased adhesion of neutrophils to vascular endothelial cells. Many diseases are characterised by massive neutrophil infiltration. Histamine release from basophils (in both atopic and normal individuals) is induced by IL-8 as is lysozomal enzyme release and respiratory burst from neutrophils.

The central role of IL-1 and TNF together with other leukocyte-derived cytokines as important and critical inflammatory mediators is well documented. The inhibition of these cytokines has been shown or would be expected to be of benefit in controlling, alleviating or reducing many of these disease states.

The central position that p38 occupies within the cascade of signalling molecules mediating extracellular to intracellular signalling, and its influence over not only IL-1, TNF and IL-8 production but also the synthesis and/or action of other pro-inflammatory proteins (e.g. IL-6, GM-CSF, COX-2, collagenase and stromelysin), make it an attractive target for inhibition by small molecule inhibitors with the expectation that such inhibition would be a highly effective mechanism for regulating the excessive and destructive

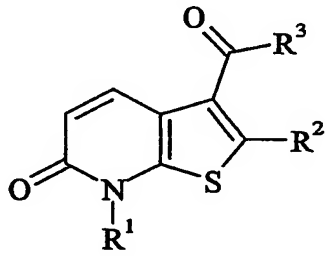
activation of the immune system. Such an expectation is supported by the potent and diverse anti-inflammatory activities described for p38 kinase inhibitors [Adams, *ibid*; Badger *et al.*, *J. Pharmacol. Exp. Ther.*, 1996, **279**, 1453-61; Griswold *et al.*, *Pharmacol. Commun.*, 1996, **7**, 323-29].

Copending international patent application no. PCT/GB03/03501 describes a series of 5-6 fused ring bicyclic heteroaromatic compounds which are stated to be potent and selective inhibitors of p38 kinase and thus of use in the prophylaxis and treatment of immune or inflammatory disorders.

The present invention provides a class of compounds which are potent and selective inhibitors of p38 kinase, especially p38α, p38β and p38β2, and splice variants thereof. The compounds in accordance with the present invention are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders.

In addition, the compounds according to the present invention may be used as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds according to this invention may be useful as radioligands in assays for detecting compounds capable of binding to the human p38 enzyme.

The present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof:



(I)

wherein

R^1 represents (C_{3-7} cycloalkyl)methyl, aryl or heteroaryl, any of which groups may be optionally substituted by one or more substituents;

R^2 represents hydrogen, cyano, $-CO_2R^a$, $-CONR^bR^c$, $-NR^bR^c$, $-NR^dCOR^a$, $-NR^dCO_2R^a$, $-NR^dCONR^bR^c$, $-NR^dSO_2R^a$ or $-NR^dCONHNHSO_2R^a$;

R^3 represents an optionally substituted aryl or heteroaryl group;

R^a represents hydrogen, C_{1-6} alkyl or C_{3-7} heterocycloalkyl (optionally substituted by C_{1-6} alkyl);

R^b represents hydrogen, C_{1-6} alkyl [optionally substituted by hydroxy, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino or C_{3-7} heterocycloalkyl], C_{2-6} alkenyl or C_{3-7} heterocycloalkyl (optionally substituted by C_{1-6} alkyl); and

R^c represents hydrogen or C_{1-6} alkyl; or

R^b and R^c, when taken together with the nitrogen atom to which they are attached, represent azetidin-1-yl [optionally substituted by hydroxy, amino, C_{1-6} alkylamino or di(C_{1-6})alkylamino], pyrrolidin-1-yl [optionally substituted by hydroxy, hydroxymethyl, amino, C_{1-6} alkylamino or di(C_{1-6})alkylamino], piperidin-1-yl [optionally substituted by hydroxy, amino, C_{1-6} alkylamino or di(C_{1-6})alkylamino], piperazin-1-yl (optionally substituted by C_{1-6} alkyl) or morpholin-4-yl; and

R^d represents hydrogen or C_{1-6} alkyl.

The compounds of formula (I) as defined above are generically encompassed within the scope of copending international patent application no. PCT/GB03/03501. However, there is no specific disclosure in that application of the precisely-defined series of thieno[2,3-*b*]pyridin-6(7*H*)-one derivatives as represented by formula (I) above.

The groups R^1 and R^3 in the compounds of formula (I) above may be unsubstituted, or substituted by one or more substituents. Typically, R^1 and/or R^3 will be unsubstituted, or substituted by one or two substituents. Suitable substituents on R^1 and/or R^3 include halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylsulphonyl, amino, aminocarbonyl and C_{2-6} alkoxycarbonyl. Typical substituents on R^1 and/or R^3 include halogen, cyano, C_{1-6} alkyl, trifluoromethyl and C_{1-6} alkoxy. Detailed substituents on R^1 and/or R^3 include halogen, C_{1-6} alkyl and C_{1-6} alkoxy.

For use in medicine, the salts of the compounds of formula (I) will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid,

maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, e.g. carboxy, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The present invention includes within its scope solvates of the compounds of formula (I) above. Such solvates may be formed with common organic solvents, e.g. hydrocarbon solvents such as benzene or toluene; chlorinated solvents such as chloroform or dichloromethane; alcoholic solvents such as methanol, ethanol or isopropanol; ethereal solvents such as diethyl ether or tetrahydrofuran; or ester solvents such as ethyl acetate. Alternatively, the solvates of the compounds of formula (I) may be formed with water, in which case they will be hydrates.

Suitable alkyl groups which may be present on the compounds according to the invention include straight-chained and branched C_{1-6} alkyl groups, for example C_{1-4} alkyl groups. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C_{1-6} alkoxy", "C_{1-6} alkylamino" and "C_{1-6} alkylsulphonyl" are to be construed accordingly.

Suitable alkenyl groups include straight-chained and branched C_{2-6} alkenyl groups, for example C_{2-4} alkenyl groups. Typical examples include vinyl, allyl and dimethylallyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

A typical (C_{3-7} cycloalkyl)methyl group is cyclopropylmethyl.

Particular aryl groups include phenyl and naphthyl, especially phenyl.

Suitable C_{3-7} heterocycloalkyl groups include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

Suitable heteroaryl groups include furyl, benzofuryl, dibenzofuryl, thienyl, benzothienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl and pyrazinyl groups.

The term "halogen" as used herein is intended to include fluorine, chlorine, bromine and iodine atoms, especially fluoro or chloro.

Where the compounds of formula (I) have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds of the invention possess two or more asymmetric centres, they may additionally exist as diastereomers. The invention is to be understood to extend to all such enantiomers and diastereomers, and to mixtures thereof in any proportion, including racemates. Formula (I) and the formulae depicted hereinafter are intended to represent all individual stereoisomers and all possible mixtures thereof, unless stated or shown otherwise. In addition, compounds of formula (I) may exist as tautomers, for example keto ($CH_2C=O$)-enol ($CH=CHOH$) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

Suitably, R^1 represents (C_{3-7} cycloalkyl)methyl or aryl, either of which groups may be optionally substituted by one or more substituents.

In one embodiment of the compounds according to the invention, R^1 represents a (C_{3-7} cycloalkyl)methyl group, especially cyclopropylmethyl.

In a favoured embodiment, R^1 represents an optionally substituted phenyl group, in particular unsubstituted, monosubstituted or disubstituted phenyl, especially unsubstituted or monosubstituted phenyl.

Examples of suitable substituents on the group R^1 include fluoro, chloro, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, trifluoromethoxy, methanesulphonyl, amino, aminocarbonyl, formyl and methoxycarbonyl.

Particular substituents on R^1 include halogen and C_{1-6} alkyl, especially chloro or methyl. A particular substituent on R^1 is halogen, especially chloro.

Illustrative values of R^1 include cyclopropylmethyl, phenyl, chlorophenyl (especially 2-chlorophenyl) and methylphenyl (especially 4-methylphenyl). Detailed values of R^1 include cyclopropylmethyl, phenyl and chlorophenyl (especially 2-chlorophenyl). A particular value of R^1 is phenyl.

Suitably, R^a represents hydrogen, C_{1-6} alkyl or C_{3-7} heterocycloalkyl.

In one embodiment, R^a represents hydrogen. In another embodiment, R^a represents C_{1-6} alkyl, especially methyl, ethyl or *tert*-butyl. In a further embodiment, R^a represents unsubstituted C_{3-7} heterocycloalkyl, especially piperidinyl (in particular piperidin-4-yl). In an additional embodiment, R^a represents C_{3-7} heterocycloalkyl

substituted by C_{1-6} alkyl, especially methylpiperidinyl (in particular 1-methylpiperidin-4-yl). Suitable values of R^a include hydrogen, methyl, ethyl, *tert*-butyl, piperidinyl (especially piperidin-4-yl) and methylpiperidinyl (especially 1-methylpiperidin-4-yl). Particular values of R^a include hydrogen, methyl, ethyl, *tert*-butyl and piperidinyl (especially piperidin-4-yl).

Suitably, R^b represents hydrogen, C_{1-6} alkyl (optionally substituted by hydroxy), C_{2-6} alkenyl or C_{3-7} heterocycloalkyl (optionally substituted by C_{1-6} alkyl).

In one embodiment, R^b represents hydrogen. In another embodiment, R^b represents unsubstituted C_{1-6} alkyl, especially methyl. In a further embodiment, R^b represents C_{1-6} alkyl substituted by hydroxy, especially 2-hydroxy-2-methylpropyl or 1-hydroxy-2-methylprop-2-yl. In a still further embodiment, R^b represents C_{1-6} alkyl substituted by C_{3-7} heterocycloalkyl, especially piperidinylethyl [in particular 2-(piperidin-1-yl)ethyl]. In a yet further embodiment, R^b represents C_{2-6} alkenyl, especially allyl. In an additional embodiment, R^b represents C_{3-7} heterocycloalkyl, which may be unsubstituted or substituted by C_{1-6} alkyl (e.g. ethyl). Suitable values of R^b include hydrogen, methyl, 2-hydroxy-2-methylpropyl, 1-hydroxy-2-methylprop-2-yl, piperidinylethyl [especially 2-(piperidin-1-yl)ethyl], allyl and ethylpyrrolidinyl (especially 1-ethylpyrrolidin-3-yl). Typical values of R^b include hydrogen, methyl, 2-hydroxy-2-methylpropyl, 1-hydroxy-2-methylprop-2-yl, allyl and ethylpyrrolidinyl (especially 1-ethylpyrrolidin-3-yl).

In one embodiment, R^c represents hydrogen. In another embodiment, R^c represents C_{1-6} alkyl, especially methyl. Suitable values of R^c include hydrogen and methyl.

Alternatively, R^b and R^c, when taken together with the nitrogen atom to which they are attached, suitably represent azetidin-1-yl, pyrrolidin-1-yl (optionally substituted by hydroxymethyl), piperidin-1-yl, piperazin-1-yl (optionally substituted by C_{1-6} alkyl) or morpholin-4-yl.

In a typical embodiment, R^b and R^c, when taken together with the nitrogen atom to which they are attached, represent azetidin-1-yl, pyrrolidin-1-yl, hydroxypyrrolidin-1-yl (especially 3-hydroxypyrrolidin-1-yl), hydroxymethyl-pyrrolidin-1-yl [especially 2-(hydroxymethyl)pyrrolidin-1-yl], piperidin-1-yl, methyl-piperazin-1-yl (especially 4-methylpiperazin-1-yl) or morpholin-4-yl. In an alternative embodiment, R^b and R^c, when taken together with the nitrogen atom to which they are attached, represent azetidin-1-yl,

pyrrolidin-1-yl, hydroxymethyl-pyrrolidin-1-yl [especially 2-(hydroxymethyl)pyrrolidin-1-yl], piperidin-1-yl, methyl-piperazin-1-yl (especially 4-methylpiperazin-1-yl) or morpholin-4-yl.

In one embodiment, R^d represents hydrogen. In another embodiment, R^d represents C_{1-6} alkyl, especially methyl. Typically, R^d is hydrogen.

Illustrative values of R^2 include hydrogen, cyano, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, (1-hydroxy-2-methylprop-2-yl)aminocarbonyl, dimethylaminocarbonyl, azetidin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, 2-(hydroxymethyl)pyrrolidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, amino, 2-(piperidin-1-yl)ethylamino, dimethylamino, azetidin-1-yl, 3-hydroxypyrrolidin-1-yl, piperidin-1-yl, acetylamino, piperidin-4-ylcarbonylamino, (1-methylpiperidin-4-yl)carbonylamino, *tert*-butoxycarbonylamino, aminocarbonylamino, (2-hydroxy-2-methylpropyl)aminocarbonylamino, dimethylaminocarbonylamino, allylaminocarbonylamino, (1-ethylpyrrolidin-3-yl)amino-carbonylamino, azetidin-1-ylcarbonylamino, 2-(hydroxymethyl)pyrrolidin-1-ylcarbonyl-amino, (4-methylpiperazin-1-yl)carbonylamino, methanesulphonylamino and methanesulphonylhydrazinylcarbonylamino.

Representative values of R^2 include hydrogen, cyano, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, (1-hydroxy-2-methylprop-2-yl)aminocarbonyl, dimethylaminocarbonyl, azetidin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, 2-(hydroxymethyl)pyrrolidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, amino, dimethylamino, azetidin-1-yl, piperidin-1-yl, acetylamino, piperidin-4-ylcarbonylamino, (1-methylpiperidin-4-yl)carbonylamino, *tert*-butoxycarbonylamino, aminocarbonylamino, (2-hydroxy-2-methylpropyl)aminocarbonylamino, dimethylaminocarbonylamino, allylaminocarbonylamino, (1-ethylpyrrolidin-3-yl)amino-carbonylamino, azetidin-1-ylcarbonylamino, 2-(hydroxymethyl)pyrrolidin-1-ylcarbonyl-amino, (4-methylpiperazin-1-yl)carbonylamino, methanesulphonylamino and methanesulphonylhydrazinylcarbonylamino.

Typical values of R^2 include hydrogen, cyano, carboxy, ethoxycarbonyl, aminocarbonyl, methylaminocarbonyl, (1-hydroxy-2-methylprop-2-yl)aminocarbonyl, dimethylaminocarbonyl, azetidin-1-ylcarbonyl, pyrrolidin-1-ylcarbonyl, 2-(hydroxymethyl)pyrrolidin-1-ylcarbonyl, morpholin-4-ylcarbonyl, amino, dimethylamino, azetidin-1-yl, piperidin-1-yl, acetylamino, piperidin-4-ylcarbonylamino, *tert*-butoxycarbonylamino, aminocarbonylamino, (2-hydroxy-2-methylpropyl)aminocarbonylamino,

dimethylaminocarbonylamino, allylaminocarbonylamino, (1-ethylpyrrolidin-3-yl)amino-carbonylamino, azetidin-1-ylcarbonylamino, 2-(hydroxymethyl)pyrrolidin-1-ylcarbonyl-amino, (4-methylpiperazin-1-yl)carbonylamino, methanesulphonylamino and methanesulphonylhydrazinylcarbonylamino.

Selected values for the substituent R^3 include phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl and tetrazolyl, any of which groups may be optionally substituted by one or more substituents.

In a favoured embodiment, R^3 represents an optionally substituted phenyl group, in particular unsubstituted, monosubstituted or disubstituted phenyl.

In another embodiment, R^3 represents optionally substituted pyridinyl, especially unsubstituted or monosubstituted pyridin-2-yl.

Examples of suitable substituents on the group R^3 include fluoro, chloro, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, methanesulphonyl, amino, aminocarbonyl and methoxycarbonyl.

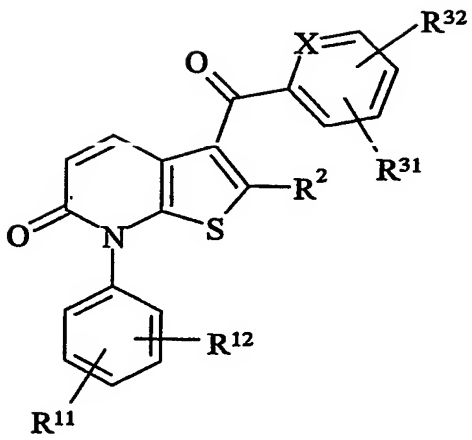
Examples of suitable substituents on R^3 include fluoro, chloro, cyano, methyl, trifluoromethyl and ethoxy. Examples of typical substituents on R^3 include fluoro, chloro, methyl, trifluoromethyl and ethoxy. Examples of individual substituents on R^3 include fluoro, chloro, methyl and ethoxy.

Suitable values of R^3 include phenyl, difluorophenyl, chlorophenyl, (chloro)-(fluoro)phenyl, cyanophenyl, methylphenyl, (fluoro)(methyl)phenyl, trifluoromethyl-phenyl, (ethoxy)(methyl)phenyl and methylpyridinyl.

Typical values of R^3 include phenyl, difluorophenyl, chlorophenyl, (chloro)-(fluoro)phenyl, methylphenyl, (fluoro)(methyl)phenyl, trifluoromethylphenyl, (ethoxy)(methyl)phenyl and methylpyridinyl.

Detailed values of R^3 include phenyl, difluorophenyl, chlorophenyl, (chloro)-(fluoro)phenyl, methylphenyl, (fluoro)(methyl)phenyl, (ethoxy)(methyl)phenyl and methylpyridinyl.

A particular sub-class of compounds according to the invention is represented by the compounds of formula (II), and pharmaceutically acceptable salts and solvates thereof:



(II)

wherein

X represents CH or N;

R^{11}, R^{12}, R^{31} and R^{32} independently represent hydrogen, halogen, cyano, nitro, C_{1-6} alkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, difluoromethoxy, trifluoromethoxy, C_{1-6} alkylsulphonyl, amino, aminocarbonyl or C_{2-6} alkoxycarbonyl; and

R^2 is as defined above.

In one embodiment, X is CH.

In another embodiment, X is N.

Suitably, R^{11}, R^{12}, R^{31} and R^{32} independently represent hydrogen, fluoro, chloro, cyano, nitro, methyl, trifluoromethyl, hydroxy, methoxy, ethoxy, difluoromethoxy, trifluoromethoxy, methanesulphonyl, amino, aminocarbonyl or methoxycarbonyl.

Illustratively, R^{11}, R^{12}, R^{31} and R^{32} independently represent hydrogen, halogen, cyano, C_{1-6} alkyl, trifluoromethyl or C_{1-6} alkoxy. Suitable values of R^{11}, R^{12}, R^{31} and R^{32} include hydrogen, fluoro, chloro, cyano, methyl, trifluoromethyl and ethoxy.

Typically, R^{11}, R^{12}, R^{31} and R^{32} independently represent hydrogen, halogen, C_{1-6} alkyl or C_{1-6} alkoxy. Particular values of R^{11}, R^{12}, R^{31} and R^{32} include hydrogen, fluoro, chloro, methyl and ethoxy.

Suitable values of R^{11} include hydrogen, halogen and C_{1-6} alkyl. Particular values of R^{11} include hydrogen and halogen. In one embodiment, R^{11} is hydrogen. In another embodiment, R^{11} represents halogen, especially chloro. In a further embodiment, R^{11} represents C_{1-6} alkyl, especially methyl.

Typically, R^{12} is hydrogen.

Suitable values of R^{31} include hydrogen, halogen, cyano, C_{1-6} alkyl and trifluoromethyl. Particular values of R^{31} include hydrogen, fluoro, chloro, cyano, methyl and trifluoromethyl.

Typical values of R^{31} include hydrogen, halogen, C_{1-6} alkyl and trifluoromethyl. Detailed values of R^{31} include hydrogen, fluoro, chloro, methyl and trifluoromethyl.

Representative values of R^{31} include hydrogen, halogen and C_{1-6} alkyl. Specific values of R^{31} include hydrogen, fluoro, chloro and methyl.

Suitable values of R^{32} include hydrogen, halogen and C_{1-6} alkoxy. Particular values of R^{32} include hydrogen, fluoro and ethoxy. In one embodiment, R^{32} is hydrogen. In another embodiment, R^{32} is fluoro.

Particularly useful compounds of the invention include each of the compounds described in the accompanying Examples, and pharmaceutically acceptable salts and solvates thereof.

Compounds according to the invention are potent and selective inhibitors of p38 kinases, including isoforms and splice variants thereof. More specifically, the compounds of the invention are inhibitors of p38α, p38β and p38β2. The ability of the compounds to act in this way may be simply determined by employing tests such as those described hereinbelow.

The compounds of formula (I) are of use in modulating the activity of p38 kinases and in particular are of use in the prophylaxis and treatment of any p38 kinase mediated diseases or disorders in a human or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders. Furthermore, the invention extends to the administration to a human of an effective amount of a p38 inhibitor for treating any such disease or disorder.

The invention also extends to the prophylaxis or treatment of any disease or disorder in which p38 kinase plays a role including conditions caused by excessive or unregulated pro-inflammatory cytokine production, including for example excessive or unregulated TNF, IL-1, IL-6 and IL-8 production in a human or other mammal. The invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such cytokine-mediated diseases or disorders. Furthermore, the invention extends to the administration to a human of an effective amount of a p38 inhibitor for treating any such disease or disorder.

Diseases or disorders in which p38 kinase plays a role either directly or via pro-inflammatory cytokines including the cytokines TNF, IL-1, IL-6 and IL-8 include without limitation autoimmune diseases, inflammatory diseases, destructive-bone disorders, proliferative disorders, neurodegenerative disorders, viral diseases, allergies, infectious diseases, heart attacks, angiogenic disorders, reperfusion/ischemia in stroke, vascular hyperplasia, organ hypoxia, cardiac hypertrophy, thrombin-induced platelet aggregation and conditions associated with prostaglandin endoperoxidase synthetase-2 (COX-2).

Autoimmune diseases which may be prevented or treated include but are not limited to rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, multiple sclerosis, diabetes, glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, hemolytic anemia, autoimmune gastritis, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, atopic dermatitis, graft vs host disease and psoriasis.

The invention further extends to the particular autoimmune disease rheumatoid arthritis.

Inflammatory diseases which may be prevented or treated include but are not limited to asthma, allergies, respiratory distress syndrome, and acute or chronic pancreatitis.

Destructive bone disorders which may be prevented or treated include but are not limited to osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

Proliferative diseases which may be prevented or treated include but are not limited to acute or chronic myelogenous leukemia, Kaposi's sarcoma, metastatic melanoma and multiple myeloma.

Neurodegenerative diseases which may be prevented or treated include but are not limited to Parkinson's disease, Alzheimer's disease, cerebral ischemias and neurodegenerative disease caused by traumatic injury.

Viral diseases which may be prevented or treated include but are not limited to acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

Infectious diseases which may be prevented or treated include but are not limited to septic shock, sepsis and Shigellosis.

In addition, p38 inhibitors of this invention exhibit inhibition of expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxidase synthetase-2,

otherwise known as cyclooxygenase-2 (COX-2), and are therefore of use in therapy. Pro-inflammatory mediators of the cyclooxygenase pathway derived from arachidonic acid are produced by inducible COX-2 enzyme. Regulation of COX-2 would regulate these pro-inflammatory mediators such as prostaglandins, which affect a wide variety of cells and are important and critical inflammatory mediators of a wide variety of disease states and conditions. In particular, these inflammatory mediators have been implicated in pain, such as in the sensitization of pain receptors, or edema. Accordingly, additional p38-mediated conditions which may be prevented or treated include edema, analgesia, fever and pain such as neuromuscular pain, headache, dental pain, arthritis pain and pain caused by cancer.

As a result of their p38 inhibitory activity, compounds of the invention have utility in the prevention and treatment of diseases associated with cytokine production including but not limited to those diseases associated with TNF, IL-1, IL-6 and IL-8 production.

TNF-mediated diseases or conditions include for example rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resportion disease, reperfusion injury, graft vs host reaction, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, AIDS, ARC or malignancy, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, and viral infections such as HIV, CMV, influenza and herpes; veterinary viral infections such as lentivirus infections, including but not limited to equine infectious anemia virus, caprine arthritis virus, visna virus or maedi virus; and retrovirus infections, including feline immunodeficiency virus, bovine immunodeficiency virus and canine immunodeficiency virus.

Compounds of the invention may also be used in the treatment of viral infections, where such viruses elicit TNF production *in vivo* or are sensitive to upregulation by TNF. Such viruses include those that produce TNF as a result of infection and those that are sensitive to inhibition, for instance as a result of decreased replication, directly or indirectly by the TNF-inhibiting compounds of the invention. Such viruses include, but are not limited to, HIV-1, HIV-2 and HIV-3, Cytomegalovirus (CMV), influenza, adenovirus and the herpes group of viruses such as *Herpes zoster* and *Herpes simplex*.

IL-1 mediated diseases or conditions include for example rheumatoid arthritis, osteoarthritis, psoriatic arthritis, traumatic arthritis, rubella arthritis, inflammatory bowel disease, stroke, endotoxemia and/or toxic shock syndrome, inflammatory reaction induced by endotoxin, diabetes, pancreatic β-cell disease, Alzheimer's disease, tuberculosis, atherosclerosis, muscle degeneration and cachexia.

IL-8 mediated diseases and conditions include for example those characterized by massive neutrophil infiltration such as psoriasis, inflammatory bowel disease, asthma, cardiac, brain and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis. The increased IL-8 production associated with each of these diseases is responsible for the chemotaxis of neutrophils into inflammatory sites. This is due to the unique property of IL-8 (in comparison to TNF, IL-1 and IL-6) of promoting neutrophil chemotaxis and activation. Therefore, inhibition of IL-8 production would lead to a direct reduction in neutrophil infiltration.

It is also known that both IL-6 and IL-8 are produced during rhinovirus (HRV) infections and contribute to the pathogenesis of the common cold and exacerbation of asthma associated with HRV infection [Turner *et al.*, *Clin. Infec. Dis.*, 1997, **26**, 840; Grunberg *et al.*, *Am. J. Crit. Care Med.*, 1997, **155**, 1362; Zhu *et al.*, *J. Clin. Invest.*, 1996, **97**, 421]. It has also been demonstrated *in vitro* that infection of pulmonary epithelial cells (which represent the primary site of infection by HRV) with HRV results in production of IL-6 and IL-8 [Sabauste *et al.*, *J. Clin. Invest.*, 1995, **96**, 549]. Therefore, p38 inhibitors of the invention may be used for the treatment or prophylaxis of the common cold or respiratory viral infection caused by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus or adenovirus.

For the prophylaxis or treatment of a p38 or pro-inflammatory cytokine mediated disease the compounds according to the invention may be administered to a human or mammal as pharmaceutical compositions, and according to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I) in association with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogenphosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles or preservatives. The preparations may also contain buffer salts, flavouring agents, colouring agents or sweetening agents, as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of formula (I) may be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoules or multi-dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (I) may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g.

dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

For topical administration the compounds according to the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds according to the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

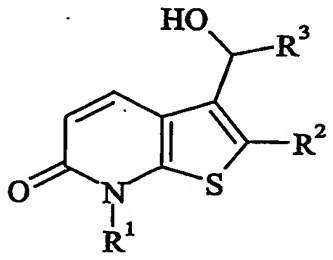
For ophthalmic administration the compounds according to the present invention may be conveniently formulated as microionized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

For rectal administration the compounds according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg, e.g. around 0.01 mg/kg to 40 mg/kg body weight for oral or buccal administration, from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to

around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

The compounds according to the invention may be prepared by a process which comprises oxidizing a compound of formula (III):

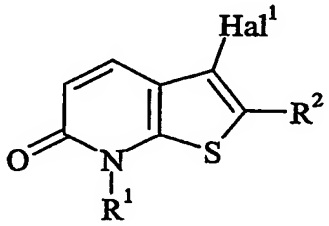


(III)

wherein R^1, R^2 and R^3 are as defined above.

Oxidation of compound (III) may be conveniently carried by treatment with an oxidizing agent such as manganese dioxide, typically at room temperature in a solvent such as dichloromethane.

The compounds of formula (III) may be prepared by reacting an aldehyde of formula R^3-CHO with a compound of formula (IV):

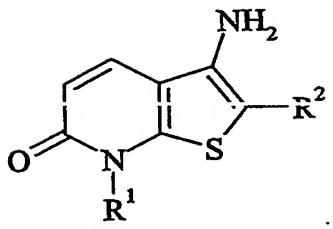


(IV)

wherein R^1, R^2 and R^3 are as defined above, and Hal^1 represents a halogen atom, e.g. bromo.

The reaction is conveniently effected by treating compound (IV) with a strong base, e.g. *n*-butyllithium or *tert*-butyllithium, followed by addition of the aldehyde of formula R^3-CHO, typically in an inert solvent such as tetrahydrofuran.

The intermediates of formula (IV) may be prepared from the corresponding amine of formula (V):

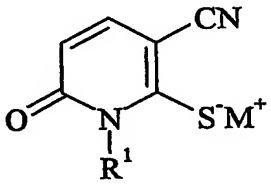


(V)

wherein R^1 and R^2 are as defined above; by diazotisation followed by halogen exchange.

Diazotisation may be conveniently effected by treating compound (V) with a nitrite, e.g. *tert*-butyl nitrite. Halogen exchange may be conveniently accomplished by reaction with a copper halide, e.g. copper(II) bromide. Advantageously, both procedures may be carried out *in situ*, typically in an inert solvent such as acetonitrile.

The intermediates of formula (V) wherein R^2 represents cyano may be prepared by reacting a compound of formula Hal^2-CH_2-CN with a compound of formula (VI):



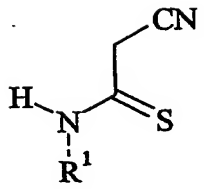
(VI)

wherein R^1 is as defined above, M^+ represents an alkali metal cation, and Hal^2 represents a halogen atom, e.g. chloro.

The alkali metal cation M^+ is suitably a sodium or potassium cation, especially Na^+.

The reaction is conveniently performed at an elevated temperature in a suitable solvent, e.g. acetonitrile.

The intermediates of formula (VI) may be prepared by reacting 1,3-dimethyluracil with a compound of formula (VII):

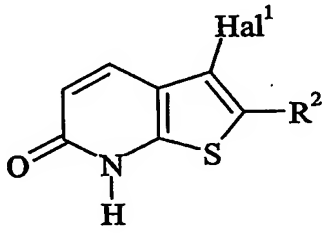


(VII)

wherein R^1 is as defined above; in the presence of an alkali metal alkoxide MOAlk, in which M is as defined above, and Alk represents C_{1-6} alkyl, e.g. methyl.

The reaction is conveniently effected in a suitable solvent, for example a C_{1-4} alkanol such as methanol or ethanol, or mixtures thereof, at an elevated temperature, for example the reflux temperature of the solvent(s) employed.

In an alternative procedure, the intermediates of formula (IV) wherein R^1 represents optionally substituted aryl may be prepared by reacting a boronic acid derivative of formula R^{1a}-$B(OH)_2$ with a compound of formula (VIII):



(VIII)

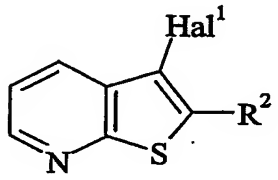
wherein R^2 and Hal^1 are as defined above, and R^{1a} represents aryl, which may be optionally substituted by one or more substituents (as defined above for R^1).

The reaction is conveniently accomplished by mixing the reagents with a copper salt, e.g. copper(II) acetate, typically in the presence of pyridine, in a suitable solvent such as dichloromethane.

In a further procedure, the intermediates of formula (IV) wherein R^1 represents optionally substituted (C_{3-7} cycloalkyl)methyl may be prepared by treating a compound of formula (VIII) as defined above with a strong base, e.g. sodium hydride; followed by reaction with a compound of formula L-R^{1b}, in which L represents a leaving group, and R^{1b} represents (C_{3-7} cycloalkyl)methyl, which may be optionally substituted by one or more substituents (as defined above for R^1).

The reaction is conveniently effected in a dipolar aprotic solvent, e.g. *N,N*-dimethylformamide.

The intermediates of formula (VIII) may be prepared by treating a compound of formula (IX):



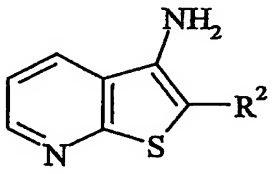
(IX)

wherein R^2 and Hal^1 are as defined above; with an oxidising agent; and subsequently rearranging the *N*-oxide derivative thereby obtained to the required compound of formula (VIII) by treatment with trifluoroacetic anhydride.

The oxidising agent employed to convert compound (IX) to the corresponding *N*-oxide derivative may suitably be a peracid such as 3-chloroperoxybenzoic acid. The reaction is conveniently accomplished by stirring in a solvent such as dichloromethane, typically at room temperature.

The trifluoroacetic anhydride-mediated rearrangement of the *N*-oxide derivative to compound (VIII) is conveniently carried out in a dipolar aprotic solvent such as *N,N*-dimethylformamide, typically at a temperature in the region of 0°C.

The intermediates of formula (IX) may be prepared from the corresponding amine of formula (X):



(X)

wherein R^2 is as defined above; by diazotisation followed by halogen exchange; under conditions analogous to those described above for the conversion of compound (V) into compound (IV).

The intermediates of formula (X) in which R^2 is an electron-withdrawing group, for example cyano or $-CO_2R^a$, may be prepared by reacting 2-chloro-3-cyanopyridine with a compound of formula R^{2a}-CH_2-SH wherein R^{2a} represents an electron-withdrawing group, e.g. cyano or $-CO_2R^a$, in which R^a is as defined above. The reaction is conveniently effected in the presence of a base such as sodium carbonate, in a suitable solvent, for example a C_{1-4} alkanol such as ethanol, typically at the reflux temperature of the solvent employed.

Where they are not commercially available, the starting materials of formula (VII) may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

It will be understood that any compound of formula (I) initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula (I) by techniques known from the art. By way of example, a compound of formula (I) wherein R^2 represents cyano may be converted into the corresponding compound wherein R^2 represents amido ($-CONH_2$) by treatment with a strong base such as sodium hydroxide, typically in refluxing aqueous ethanol. Similarly, a compound of formula (I) wherein R^2 represents $-CO_2R^a$, in which R^a is other than hydrogen, may be converted into the corresponding compound in which R^2 is carboxy ($-CO_2H$) by treatment with a strong base such as sodium hydroxide, typically in refluxing aqueous ethanol. A compound of formula (I) wherein R^2 represents $-CO_2H$ may be decarboxylated to the corresponding compound wherein R^2 is hydrogen by treatment with a strong mineral acid, e.g. concentrated hydrochloric acid. A compound of formula (I) wherein R^2 represents $-CO_2H$ may be converted into the corresponding compound wherein R^2 represents $-CONR^aR^b$ by reaction with an amine of formula H-NR^aR^b in the presence of a condensing agent such as EDC (*vide infra*), a triazole additive such as HOBT (*vide infra*) and a morpholine derivative such as NMM (*vide infra*). A compound of formula (I) wherein R^2 represents $-CO_2H$ may be converted into the corresponding compound wherein R^2 represents $-NHCO_2R^a$ by treatment with diphenylphosphoryl azide at an elevated temperature in the presence of the requisite alcohol of formula R^a-OH and an organic base such as triethylamine. A compound of formula (I) wherein R^2 represents *tert*-butoxycarbonylamino may be converted into the corresponding compound wherein R^2 is amino ($-NH_2$) by treatment with a strong organic acid such as trifluoroacetic acid. A compound of formula (I) wherein R^2 represents $-NH_2$ may be converted into the

corresponding compound wherein R^2 represents halogen, e.g. bromo, by diazotisation followed by halogen exchange, under conditions analogous to those described above for the conversion of compound (V) into compound (IV); the resulting halo derivative may in turn be converted into the corresponding compound wherein R^2 represents $-NR^aR^b$, in which R^a and/or R^b is other than hydrogen, by reaction with the appropriate amine of formula $H-NR^aR^b$ in the presence of a transition metal catalyst such as tris(dibenzylidene-acetone)palladium(0), ideally in the presence of a ligand such as BINAP (*vide infra*) and a base such as caesium carbonate, typically at an elevated temperature in a suitable solvent, e.g. toluene. A compound of formula (I) wherein R^2 represents $-NH_2$ may be converted into the corresponding compound wherein R^2 represents $-NHCOR^a$ by reaction with a carboxylic acid of formula R^aCO_2H, or an acid anhydride of formula $(R^aCO)_2O$, suitably in the presence of an acylation catalyst such as 4-dimethylaminopyridine. Alternatively, a compound of formula (I) wherein R^2 represents $-NH_2$ may be converted into the corresponding compound wherein R^2 represents $-NHCOR^a$ by reaction with a carboxylic acid of formula R^aCO_2H in the presence of a condensing agent such as EDC, a triazole additive such as HOBT and a morpholine derivative such as NMM. A compound of formula (I) wherein R^2 represents $-NH_2$ may be converted into the corresponding compound wherein R^2 represents -NHCOCl by treatment with phosgene, typically in the presence of an organic amine such as triethylamine; the resulting compound may in turn be converted into the corresponding compound wherein R^2 represents $-NHCONR^aR^b$ by reaction with the appropriate amine of formula $H-NR^aR^b$. Similarly, a compound of formula (I) wherein R^2 represents $-NH_2$ may be converted into the corresponding compound wherein R^2 represents -NHCOCl by treatment with phosgene, as before; the resulting compound may in turn be converted into the corresponding compound wherein R^2 represents $-NHCONHNHSO_2R^a$ by reaction with the appropriate hydrazine derivative of formula $R^aSO_2NHNH_2$. A compound of formula (I) wherein R^2 represents *tert*-butoxycarbonylamino may be converted into the corresponding compound wherein R^2 represents $-N(SO_2R^a)[CO_2C(CH_3)_3]$ by treatment with a strong base, e.g. sodium bis(trimethylsilyl)amide, and then with the appropriate sulphonyl halide derivative, for instance a sulphonyl chloride derivative of formula R^aSO_2Cl; the resulting compound may in turn be converted into the corresponding compound wherein R^2 represents $-NHSO_2R^a$ by deprotection using a strong organic acid such as trifluoroacetic acid.

Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques. In particular, where it is desired to obtain a particular enantiomer of a compound of formula (I) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers. Thus, for example, diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (I), e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation, and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt. In another resolution process a racemate of formula (I) may be separated using chiral HPLC. Moreover, if desired, a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above. Alternatively, a particular enantiomer may be obtained by performing an enantiomer-specific enzymatic biotransformation, e.g. an ester hydrolysis using an esterase, and then purifying only the enantiomerically pure hydrolysed acid from the unreacted ester antipode. Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed, J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at any convenient subsequent stage utilising methods known from the art.

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

NMM - *N*-methylmorpholine; EtOAc - ethyl acetate;
MeOH - methanol; BOC - *tert*-butoxycarbonyl;
DCM - dichloromethane; AcOH - acetic acid;
DMF - *N*,*N*-dimethylformamide; EtOH - ethanol;
DMSO - dimethylsulphoxide; iPr - isopropyl;
Et_2O - diethyl ether; Me - methyl;
THF - tetrahydrofuran; h - hour;
MCPBA - 3-chloroperoxybenzoic acid; r.t. - room temperature;
EDC - 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride;
HOBT - 1-hydroxybenzotriazole hydrate;
BINAP - 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl;
m.p. - melting point; aq - aqueous;
sat. - saturated.

All NMRs were obtained either at 300 MHz or 400 MHz.

Compounds were named with the aid of ACD Labs Name (v. 6.0) supplied by Advanced Chemical Development, Toronto, Canada.

LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100 LC/MS using the following method: Phenomenex Luna 3μ $C_{18}(2)$ 50 x 4.6 mm column; mobile phase A = 0.1% formic acid in water; mobile phase B = 0.1% formic acid in MeCN; flow rate of 0.9 $mlmin^{-1}$; column temperature 40°C.

Gradient:

Time (min)	%B
Initial	5
2.0	95
3.0	95
5.0	5
5.5	end

Where stated alternative LCMS conditions (Conditions B) were used: LCMS retention times (RT) quoted were generated on a Hewlett Packard 1100/ThermoFinnigan LCQ Duo LC/MS system using Electrospray ionisation and the following LC method: Phenomenex Luna 5µ $C_{18}(2)$ 100 x 4.6 mm column; mobile phase A = 0.08% formic acid in water; mobile phase B = 0.08% formic acid in MeCN; flow rate of 3.0 $mlmin^{-1}$; column temperature 35°C.

Gradient:

Time (min)	%B
0.00	5
4.40	95
5.30	95
5.32	5
6.50	5

INTERMEDIATE 1

Ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of 2-chloro-3-cyanopyridine (330 g, 2.38 mol), ethyl 2-mercaptoacetate (361.2 g, 3.01 mol), sodium carbonate (265 g, 2.5 mol) and EtOH (1.2 l) was heated to reflux for 4.5 h. The reaction mixture was then cooled to ambient temperature and added to water (15 l). The resulting slurry was stirred for 0.5 h then filtered. The filter cake was washed with two portions of water (2 x 2.5 l). The solids were then dried to constant weight under vacuum at 45°C to yield the *title compound* as a brown solid (493 g, 93%). δ_H ($CDCl_3$) 8.68 (1H, dd, *J* 4.7, 1.2 Hz), 7.93 (1H, dd, *J* 8.5, 1.2 Hz), 7.29 (1H, dd, *J* 8.5, 4.7 Hz), 5.90 (2H, br), 4.38 (2H, q, *J* 7.0 Hz), 1.40 (3H, t, *J* 7.0 Hz). LCMS RT 2.9 minutes, 223 $(M+H)^+$.

INTERMEDIATE 2

Ethyl 3-bromothieno[2,3-*b*]pyridine-2-carboxylate

Intermediate 1 (363.6 g, 1.64 mol) was added in portions over two hours to a mixture of copper(II) bromide (403.3 g, 1.81 mol), *tert*-butyl nitrite (220.6 g, 2.15 mol) and acetonitrile (3.6 l) with stirring and maintaining a temperature of between 20 and 25°C. The mixture was then stirred at 20°C for 2 hours before it was slowly added to 2M HCl(aq) (4.2 l). The reaction mixture slurry was filtered and the solids were washed with water (500 ml). The combined filtrate was extracted with ethyl acetate (8 l) and this ethyl acetate solution was washed with 2M HCl(aq) (2.2 l). The filtered solids were also dissolved in ethyl acetate (6 l) and this solution was washed twice with 2M HCl(aq) (4.4 l and 2.2 l). The combined ethyl acetate solutions were washed with 2M HCl(aq) (2.2 l) and water (2 x 2 l), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a solid residue. This was broken up and dried to constant weight under vacuum at 45°C to yield the *title compound* as a brown solid (458.5 g, 98%). δ_H (DMSO-d_6) 8.89 (1H, d, *J* 4.7 Hz), 8.47 (1H, d, *J* 8.6 Hz), 7.71 (1H, dd, *J* 8.6, 4.7 Hz), 4.46 (2H, q, *J* 7.2 Hz), 1.40 (3H, t, *J* 7.2 Hz). LCMS RT 3.8 minutes, 288 $(M+H)^+$.

INTERMEDIATE 3

Ethyl 3-bromothieno[2,3-*b*]pyridine-2-carboxylate *N*-oxide

MCPBA (240 g @ 70% = 168 g, 0.97 mol) was added portionwise over 0.5 h to a slurry of Intermediate 2 (214 g, 0.747 mol) in DCM (2140 ml) under nitrogen and the mixture then stirred at room temperature for 18 h. The reaction mixture was quenched with water (800 ml) and pH adjusted to 8.5 with 10% w/v sodium carbonate solution (1250 ml). The basic aqueous layer was removed and the organic layer washed with water until pH 7. The organic layer was concentrated *in vacuo* and the crude *title product* was recovered as a tan solid. The crude product was purified by slurrying in *tert*-butyl methyl ether (600 ml) for 1 h at 0-5°C to give the *title compound* (174 g, 77%). δ_H ($CDCl_3$) 8.44 (1H, dd, *J* 6.2, 0.8 Hz), 7.87 (1H, dd, *J* 8.3, 0.8 Hz), 7.48 (1H, dd, *J* 8.3, 6.2 Hz), 4.49 (2H, q, *J* 7.1 Hz), 1.48 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 2.61 minutes, 302 $(M+H)^+$.

INTERMEDIATE 4

Ethyl 3-bromo-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

Trifluoroacetic anhydride (3.49 g, 2.36 ml, 16.6 mmol) was added to a mixture of Intermediate 3 (500 mg, 1.66 mmol) and DMF (10 ml) at 0°C under nitrogen. After stirring for 16 h the volatiles were removed *in vacuo* and the residue co-evaporated with toluene (2 x 20 ml). The crude material was then extracted with EtOAc (2 x 100 ml). The EtOAc extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by slurrying in toluene (10 ml) to give the *title compound* as a beige solid (260 mg, 52%). δ_H (DMSO-d_6) 12.20 (1H, br s), 7.75 (1H, d, *J* 9.0 Hz), 6.50 (1H, d, *J* 9.0 Hz), 4.15 (2H, q, *J* 7.1 Hz), 1.12 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 2.86 minutes, 302 $(M+H)^+$.

INTERMEDIATE 5

Ethyl 3-bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 4 (302 mg, 1.00 mmol), copper(II) acetate (278 mg, 1.50 mmol), phenylboronic acid (488 mg, 4.00 mmol), DCM (5 ml) and pyridine (158 mg, 2.00 mmol) was stirred at room temperature for 18 h with the exclusion of moisture. The reaction was then diluted with DCM (50 ml), washed with 2M HCl(aq) (50 ml) and the aqueous re-extracted with DCM (50 ml). The combined organics were then washed with water (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by trituration with MeOH (12 ml), to give the *title compound* as a beige solid (270 mg, 72%). δ_H ($CDCl_3$) 7.82 (1H, d, *J* 8.5 Hz), 7.70-7.62 (3H, m), 7.54-7.42 (2H, m), 6.70 (1H, d, *J* 8.5 Hz), 4.15 (2H, q, *J* 7.1 Hz), 1.14 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 3.75 minutes, 378 $(M+H)^+$. m.p. 201.6-206.0°C.

INTERMEDIATE 6

Sodium 3-cyano-6-oxo-1-phenyl-1,6-dihydropyridine-2-thiolate

A solution of sodium methoxide in MeOH (30 wt %, 202.2 g) was added to absolute EtOH (360 ml) followed by 1,3-dimethyluracil (75 g) and 2-cyano-*N*-phenyl-thioacetamide (Adhikari *et al.*, *Australian J. Chem.*, 1999, **52**, 63-67) (90 g). The resulting mixture was heated at reflux for 8 h and then allowed to cool to ambient temperature overnight. The reaction mixture was then cooled to +5°C and maintained at this temperature for at least an hour when the product was recovered by filtration. The

filter cake was washed with cold (+5°C) absolute ethanol (450 ml) and then dried to constant weight under vacuum at 45°C to give the *title compound* as a pale pink solid (130.0 g). The product thus obtained contained residual EtOH and MeOH, estimated at 12.2 wt % by ^{1}H NMR, corresponding to a corrected yield of 114.1 g. δ_H (DMSO-d_6) 7.32 (2H, m), 7.27-7.18 (1H, m), 7.16 (1H, d, *J* 9.1 Hz), 6.92 (2H, m), 5.63 (1H, d, *J* 9.1 Hz). LCMS (Conditions B) (ES^+) RT 2.43 minutes, 229 $(M+H)^+$.

INTERMEDIATE 7

3-Amino-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

A mixture of Intermediate 6 (100 g, 0.4 mol) and chloroacetonitrile (30.4 ml, 0.48 mol) in acetonitrile (500 ml) was heated at reflux for 2 h. The mixture was cooled, initially to 40°C when water (300 ml) was added, and then to +10°C. The reaction was maintained at +10°C for at least 1 h, then the product was recovered by filtration. The filter cake was washed with cold (+10°C) water (500 ml) followed by a cold (+10°C) mixture of acetonitrile and water (1:1, 300 ml). The product was dried under vacuum at 50°C to constant weight to give the *title compound* as an off-white solid (100.9 g, 94%). δ_H (DMSO-d_6) 7.90 (1H, d, *J* 9.6 Hz), 7.46-7.33 (3H, m), 7.25 (2H, m), 6.95 (2H, br s), 6.35 (1H, d, *J* 9.6 Hz). LCMS (Conditions B) (ES^+) RT 2.69 minutes, 268 $(M+H)^+$.

INTERMEDIATE 8

3-Bromo-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

Intermediate 7 (20 g, 75 mmol) was added portionwise to a mixture of anhydrous copper(II) bromide (23.4 g, 105 mmol) and *tert*-butyl nitrite (14.8 ml, 125 mmol) in acetonitrile (600 ml) at room temperature at such a rate as to keep the internal temperature below 25°C. The addition took approximately 1 hour. After a further 0.5 h the reaction mixture was poured onto 1M HCl (500 ml) and the mixture extracted with dichloromethane (2 x 400 ml). The combined organic extracts were then washed with 1M HCl (3 x 300 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The resulting crude product was then recrystallised from methyl isobutyl ketone (700 ml). The product was dried under vacuum at 50°C to constant weight to give the *title compound* as a light brown solid

(15.14 g, 61%). δ_H ($CDCl_3$) 7.75 (1H, d, *J* 8.5 Hz), 7.55-7.70 (3H, m), 7.35 (2H, m), 6.80 (1H, d, *J* 8.5 Hz). LCMS (Conditions B) (ES^+) RT 3.54 minutes, no parent ion observed.

INTERMEDIATE 9

Ethyl 3-bromo-7-(cyclopropylmethyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

Sodium hydride (60% in mineral oil, 3.27 g, 81.4 mmol) was added in portions to a solution of Intermediate 4 (22.3 g, 74 mmol) in DMF (300 ml) at 0°C. The mixture was stirred at r.t. for 30 minutes then cyclopropylmethyl bromide (10 g, 74 mmol) was added slowly. On complete addition the mixture was heated at 60°C overnight. The reaction was cooled to r.t., DMF was removed *in vacuo* and the residue partitioned between EtOAc and brine. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 0% to 10% EtOAc in DCM) gave the *title compound* as a yellow solid (12.5 g, 47%). δ_H ($CDCl_3$) 7.57 (1H, d, *J* 9.5 Hz), 6.47 (1H, d, *J* 9.5 Hz), 4.22 (2H, q, *J* 7.0 Hz), 3.87 (2H, d, *J* 7.1 Hz), 1.26-1.19 (4H, m), 0.43-0.37 (4H, m). LCMS (ES^+) RT 3.80 minutes, 357 $(M+H)^+$.

INTERMEDIATE 10

3-Amino-7-(2-chlorophenyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

Acetonitrile (10 ml) was added to a solution of sodium bis(trimethylsilyl)amide (100 ml, 1.0M in THF, 100 mmol) in THF (50 ml) at -78°C to give a thick white precipitate. 2-Chlorophenyl isothiocyanate (7.72 g, 45.45 mmol) was added to give a brown solution. The mixture was allowed to warm to r.t. over 1 h then diluted with EtOH (50ml). 1,3-Dimethyluracil (6.4 g, 45 mmol) was added and the mixture heated at reflux for 24 h. Volatiles were removed *in vacuo* and the residue dissolved in acetonitrile (100 ml). Chloroacetonitrile (2.85 ml, 45 mmol) was added and the mixture heated at 50°C for 1 h, a second charge of chloroacetonitrile (2.85 ml, 45 mmol) was added and heating continued for 1.5 h. Some of the acetonitrile (~50 ml) was removed *in vacuo* and water was added to precipitate the product. The brown solid was filtered off, washed with water (50 ml) and Et_2O (50 ml) and dried to give the *title compound* as a brown solid (14.3 g, quantitative). δ_H (DMSO-d_6) 8.10 (1H, d, *J* 9.7 Hz), 7.75-7.73 (1H, m), 7.65-7.54 (3H,

m), 7.14 (2H, br s, NH_2), 6.54 (1H, d, *J* 9.7 Hz). LCMS (ES^+) RT 2.97 minutes, 302 $(M+H)^+$.

INTERMEDIATE 11

3-Bromo-7-(2-chlorophenyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

Intermediate 10 (1.17 g, 3.88 mmol) was suspended in acetonitrile (20 ml). Copper(II) bromide (953 mg, 4.27 mmol) was added, followed by *tert*-butyl nitrite (0.64 ml, 5.43 mmol). The mixture was stirred at r.t. for 3 h then partitioned between 2M HCl(aq) (100 ml) and EtOAc (100 ml). The organic layer was washed with 2M HCl(aq) (50 ml), 2M NaOH(aq) (50 ml) and water (25 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (silica, 0 to 5% EtOAc in DCM) gave the *title compound* as a pale brown solid (980 mg, 67%). δ_H ($CDCl_3$) 7.70 (1H, d, *J* 9.7 Hz), 7.61 (1H, dd, *J* 1.7, 7.7 Hz), 7.52-7.44 (2H, m), 7.34 (1H, dd, *J* 1.7, 7.7 Hz), 6.70 (1H, d, *J* 9.7 Hz). LCMS (ES^+) RT 3.56 minutes, 365 $(M+H)^+$.

INTERMEDIATE 12

Ethyl 3-[hydroxy(3-methylphenyl)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A solution of Intermediate 5 (5.0 g, 13.0 mmol) in THF (500 ml) was cooled to -110°C under nitrogen and *n*-BuLi (6.4 ml of a 2.5M solution in hexanes, 16 mmol) was added slowly. A solution of 3-methylbenzaldehyde (2.38 g, 20 mmol) in THF (5 ml) was added, the reaction mixture was warmed to -50°C and $NaHCO_3$(aq) (500 ml) added. The mixture was extracted with DCM (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (silica, 0-30% EtOAc in DCM) to give the *title compound* as a light tan solid (2.84 g, 52%). δ_H ($CDCl_3$) 7.86 (1H, d, *J* 9.8 Hz), 7.56-7.47 (3H, m), 7.33 (2H, d, *J* 7.1 Hz), 7.18-7.11 (4H, m), 7.02 (1H, d, *J* 7.1 Hz), 6.57 (1H, s), 6.53 (1H, d, *J* 9.8 Hz), 4.20 (2H, q, *J* 7.1 Hz), 2.28 (3H, s), 1.21 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 3.61 minutes, 420 $(M+H)^+$.

INTERMEDIATE 13

3-[Hydroxy(3-methylphenyl)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

Intermediate 8 (520 mg, 1.57 mmol) was dissolved in THF (30 ml) and cooled to -100°C. *n*-BuLi (0.70 ml of 2.5M solution in hexanes, 1.7 mmol) was added dropwise. The red solution was stirred at -100°C for 30 minutes before the addition of a solution of 3-methylbenzaldehyde (0.28 ml, 2.34 mmol) in THF (10 ml). The reaction mixture was allowed to warm to -30°C before addition of water (50 ml). The aqueous layer was extracted with DCM (2 x 100 ml) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (silica, 10-20% EtOAc in DCM) to give the *title compound* as a white solid (163 mg, 28%). δ_H ($CDCl_3$) 7.90 (1H, d, *J* 9.7 Hz), 7.55-7.45 (3H, m), 7.30-7.18 (5H, m), 7.05 (1H, m), 6.51 (1H, d, *J* 9.7 Hz), 6.13 (1H, d, *J* 3.2 Hz), 2.96 (1H, d, *J* 3.2 Hz), 2.11 (3H,s). LCMS (ES^+) RT 3.38 minutes, 373 $(M+H)^+$.

INTERMEDIATE 14

2-Bromo-3-(3-methylbenzoyl)-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

Example 4 (700 mg, 1.94 mmol) was dissolved in acetonitrile (10 ml). Copper(II) bromide (499 mg, 2.14 mmol) was added to the reaction mixture at r.t., followed by dropwise addition of a solution of *tert*-butyl nitrite (0.28 ml, 2.3 mmol) in acetonitrile (5ml). The solution was stirred for 4 h and then poured into 2M HCl(aq) (100 ml). The aqueous layer was extracted with DCM (2 x 100 ml) and the combined organic layers combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was partially purified by chromatography on silica (0-20% EtOAc in DCM) to give the *title compound* as a brown solid (250 mg of 75% pure material by LC, 23% yield). RT 4.83 minutes. This intermediate was typically used without further purification in subsequent reactions.

INTERMEDIATE 15

Ethyl 3-[hydroxy(phenyl)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

From Intermediate 5 and benzaldehyde by the method of Intermediate 12. Off-white solid. δ_H ($CDCl_3$) 7.96 (1H, d, *J* 10 Hz), 7.52-7.70 (3H, m), 7.25-7.50 (7H, m), 6.69 (1H, s), 6.62 (1H, d, *J* 10 Hz), 4.29 (2H, q, *J* 7 Hz), 1.36 (3H, t, *J* 7 Hz). LCMS (ES^+) RT 3.56 minutes, 406 $(M+H)^+$.

INTERMEDIATE 16

tert-Butyl (3-benzoyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)(methylsulfonyl)carbamate

A solution of Example 12 (100 mg, 0.22 mmol) in THF (5 ml) was cooled to -78°C under nitrogen and sodium bis(trimethylsilyl)amide (0.24 ml of a 1.0M solution in THF, 0.24 mmol) was added slowly. The reaction mixture was warmed to r.t., methanesulphonyl chloride (0.25 mg, 0.22 mmol) was added, and the mixture stirred at r.t. for 18 h. 2M HCl(aq) (10 ml) was added, and the mixture was extracted with DCM (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was taken on to the next step. LCMS (ES^+) RT 3.59 minutes, 525 $(M+H)^+$.

INTERMEDIATE 17

tert-Butyl [3-(3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl](methylsulfonyl)carbamate

From Example 3 by the method of Intermediate 16. Dark yellow solid. LCMS (ES^+) RT 3.75 minutes, 539 $(M+H)^+$.

INTERMEDIATE 18

Benzyl 3-[({[3-(3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]amino}carbonyl)amino]pyrrolidine-1-carboxylate

From Example 4 and 3-aminopyrrolidine 1-carboxylic acid benzyl ester (242 mg, 1.1 mmol), by the method of Example 20, to give the *title compound* as a yellow solid (258 mg, 77%). LCMS (ES^+) RT 3.66 minutes, 607 $(M+H)^+$.

INTERMEDIATE 19

3-[Hydroxy(phenyl)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

Intermediate 8 (520 mg, 1.57 mmol) was dissolved in THF (30 ml) and cooled to -100°C. *n*-BuLi (2.5M in hexanes, 0.75 ml, 1.9 mmol) was added dropwise with the internal temperature kept below -95°C. The red solution was stirred at -100°C for 30 minutes before the addition of a solution of benzaldehyde (0.24 ml, 2.4 mmol) in THF (10 ml). The reaction mixture was allowed to warm to room temperature before addition of water (50 ml). The aqueous layer was extracted with DCM (2 x 100 ml) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (10-20% EtOAc in DCM) to give the *title compound* as a white solid (140 mg, 25%). δ_H ($CDCl_3$) 7.90 (1H, d, *J* 9.8 Hz), 7.57-7.23 (10H, m), 6.52 (1H, d, *J* 9.8 Hz), 6.18 (1H, d, *J* 3.7 Hz), 2.89 (1H, br s). LCMS (ES^+) RT 3.24 minutes, 359 $(M+H)^+$.

INTERMEDIATE 20

Ethyl 7-(cyclopropylmethyl)-3-[hydroxy(phenyl)methyl]-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A solution of Intermediate 9 (1.0 g, 2.81 mmol), and benzaldehyde (0.45 ml, 4.22 mmol) in anhydrous THF (100 ml) under nitrogen was cooled to -78°C. *tert*-Butyllithium (3.47 ml, 1.7M in pentane, 5.9 mmol) was added dropwise and the red solution allowed to stir at -78°C for one hour. The solution was allowed to warm to -10°C before the reaction was quenched by the addition of 10% aqueous ammonium chloride solution (250 ml). The mixture was extracted with DCM (3 x 100 ml), the organics washed with brine (2 x 200 ml), dried ($MgSO_4$), filtered and the solvents removed *in vacuo*. The crude residue was purified by chromatography on silica (0-15% EtOAc in DCM) to give the *title compound* as an off-white solid (452 mg, 42%). δ_H ($CDCl_3$) 7.77 (1H, d, *J* 9.7 Hz), 7.34-7.32 (2H, m), 7.28-7.22 (2H, m), 7.20-7.17 (1H, m), 6.57 (1H, d, *J* 8.1 Hz), 6.44 (1H, d, *J* 9.7 Hz), 4.63 (1H, d, *J* 8.1 Hz), 4.33-4.22 (2H, m), 3.97 (2H, d, *J* 7.2 Hz), 1.35-1.28 (1H,

m), 1.31 (3H, t, *J* 7.1 Hz), 0.54-0.48 (4H, m). LCMS (ES^+) RT 3.59 minutes, 384 $(M+H)^+$.

INTERMEDIATE 21

7-(2-Chlorophenyl)-3-[hydroxy(phenyl)methyl]-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 11 (5 g, 13.7 mmol) and benzaldehyde (2.1 ml, 21 mmol) by the method of Intermediate 13. White solid (363 mg, 7%). δ_H ($CDCl_3$) 7.90 (1H, d, *J* 9.8 Hz), 7.60-7.58 (1H, m), 7.49-7.41 (4H, m), 7.37-7.27 (4H, m), 6.52 (1H, d, *J* 9.8 Hz), 6.19 (1H, s). LCMS (ES^+) RT 3.73 minutes, 393 $(M+H)^+$.

INTERMEDIATE 22

3-[(3-Chlorophenyl)(hydroxy)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 8 (250 mg, 0.75 mmol) and 3-chlorobenzaldehyde (0.12 ml, 1.13 mmol) by the method of Intermediate 13. White solid (224 mg, 76%). δ_H ($CDCl_3$) 7.83 (1H, d, *J* 9.8 Hz), 7.55-7.46 (4H, m), 7.38 (1H, s) 7.28-7.20 (5H, m), 6.48 (1H, d, *J* 9.8 Hz), 6.06 (1H, s). LCMS (ES^+) RT 3.48 minutes, 393 $(M+H)^+$.

INTERMEDIATE 23

3-(3-Chlorobenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 22 (224 mg, 0.57 mmol) and manganese(IV) oxide (191 mg, 2.2 mmol) by the method of Example 5. White solid (53 mg, 24%). δ_H ($CDCl_3$) 7.82-7.81 (1H, m), 7.73-7.68 (2H, m), 7.62-7.52 (4H, m) 7.43 (1H, t, *J* 7.9 Hz), 7.37-7.34 (2H, m), 6.66 (1H, d, *J* 9.8 Hz). LCMS (ES^+) RT 3.67 minutes, 391 $(M+H)^+$.

INTERMEDIATE 24

Ethyl 3-[(3-chlorophenyl)(hydroxy)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

From Intermediate 5 (5.0 g, 13 mmol) and 3-chlorobenzaldehyde (1.7 ml, 15 mmol) by the method of Intermediate 12 to give the *title compound* as an off-white solid (1.8 g, 40%). δ_H (MeOD-d_3) 8.02 (1H, d, *J* 9.7 Hz), 7.48-7.38 (3H, m), 7.31 (1H, s), 7.23-7.16 (3H, m), 7.10-7.00 (2H, m), 6.83 (1H, s), 6.29 (1H, d, *J* 9.7 Hz), 4.09 (2H, q, *J* 7.1 Hz), 1.07 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 3.70 minutes, 440 $(M+H)^+$.

INTERMEDIATE 25

3-[(2,4-Difluorophenyl)(hydroxy)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 8 (250 mg, 0.75 mmol) and 2,4-difluorobenzaldehyde (0.12 ml, 1.13 mmol) by the method of Intermediate 13. White solid (41 mg, 14%). δ_H ($CDCl_3$) 7.84 (1H, d, *J* 9.7 Hz), 7.56-7.28 (9H, m), 6.56 (1H, d, *J* 9.7 Hz), 6.36 (1H, br s). LCMS (ES^+) RT 3.30 minutes, 395 $(M+H)^+$.

INTERMEDIATE 26

3-(2,4-Difluorobenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 25 (41 mg, 0.10 mmol) and manganese(IV) oxide (41 mg, 0.47 mmol) by the method of Example 5. White solid (14 mg, 36%). δ_H ($CDCl_3$) 7.95 (1H, d, *J* 9.8 Hz), 7.75-7.70 (1H, m), 7.60-7.51 (3H, m), 7.37-7.34 (2H, m), 7.04-6.99 (1H, m), 6.91-6.85 (1H, m), 6.70 (1H, d, *J* 9.8 Hz). LCMS (ES^+) RT 3.55 minutes, 393 $(M+H)^+$.

INTERMEDIATE 27

3-[(4-Fluoro-3-methylphenyl)(hydroxy)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 8 (250 mg, 0.75 mmol) and 4-fluoro-3-methylbenzaldehyde (0.14 ml, 1.13 mmol) by the method of Intermediate 13. White solid (138 mg, 47%). δ_H ($CDCl_3$) 7.87 (1H, d, *J* 9.8 Hz), 7.57-7.41 (3H, m), 7.30-7.28 (2H, m), 7.23-7.19 (3H, m), 6.96 (1H, t, *J* 8.8 Hz), 6.53 (1H, d, *J* 9.7 Hz), 6.13 (1H, s), 2.22 (3H, s). LCMS (ES^+) RT 3.46 minutes, 391 $(M+H)^+$.

INTERMEDIATE 28

3-(4-Fluoro-3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 27 (138 mg, 0.35 mmol) and manganese(IV) oxide (138 mg, 1.6 mmol) by the method of Example 5. White solid (89 mg, 65%). δ_H ($CDCl_3$) 7.75-7.51 (6H, m), 7.37-7.34 (2H, m), 7.08 (1H, t, *J* 8.8 Hz), 6.64 (1H, d, *J* 9.7 Hz), 2.29 (3H, s). LCMS (ES^+) RT 3.68 minutes, 389 $(M+H)^+$.

INTERMEDIATE 29

Ethyl 3-[(4-fluoro-3-methylphenyl)(hydroxy)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

From Intermediate 5 and 4-fluoro-3-methylbenzaldehyde by the method of Intermediate 12. LC RT 3.58 minutes.

INTERMEDIATE 30

3-[(3-Chloro-4-fluorophenyl)(hydroxy)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 8 (250 mg, 0.75 mmol) and 3-chloro-4-fluorobenzaldehyde (179 mg, 1.13 mmol) by the method of Intermediate 13. White solid (182 mg, 59%). LCMS (ES^+) RT 3.64 minutes, 411 $(M+H)^+$.

INTERMEDIATE 31

3-(3-Chloro-4-fluorobenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 30 (182 mg, 0.44 mmol) and manganese(IV) oxide (182 mg, 2.1 mmol) by the method of Example 5. White solid (22 mg, 12%). δ_H ($CDCl_3$) 7.94 (1H, dd, *J* 2.2, 6.9 Hz), 7.76-7.72 (2H, m), 7.61-7.54 (3H, m), 7.37-7.35 (2H, m), 7.25 (1H, t, *J* 8.4 Hz), 6.68 (1H, d, *J* 9.7 Hz). LCMS (ES^+) RT 3.71 minutes, 409 $(M+H)^+$.

INTERMEDIATE 32

Ethyl 3-[hydroxy(6-methylpyridin-2-yl)methyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

From Intermediate 5 (5.0 g, 13.3 mmol) and 6-methyl-2-pyridinecarboxaldehyde (2.42 g, 2.0 mmol) by the method of Intermediate 12. White solid (2.30 g, 42%). δ_H ($CDCl_3$) 7.82 (1H, d, *J* 9.8 Hz), 7.51-7.46 (4H, m), 7.29 (2H, m), 7.02 (2H, t, *J* 7.0 Hz), 6.89 (1H, s), 6.41 (1H, d, *J* 9.8 Hz), 6.01 (1H, br s), 4.32-4.19 (2H, m), 2.57 (3H, s), 1.25 (3H, t, *J* 7.0 Hz). LCMS (ES^+) RT 2.86 minutes, 421 $(M+H)^+$.

INTERMEDIATE 33

Ethyl 3-[(6-methylpyridin-2-yl)carbonyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

From Intermediate 32 (2.30 g, 5.5 mmol) and manganese(IV) oxide (2.30 g, 26 mmol) by the method of Example 1. White solid (1.80 g, 79%). δ_H ($CDCl_3$) 7.95 (1H, d, *J* 7.6 Hz), 7.72 (1H, t, *J* 7.6 Hz), 7.58-7.48 (4H, m), 7.40-7.32 (2H, m), 7.26 (1H, d, *J* 7.6 Hz), 6.58 (1H, d, *J* 9.7 Hz), 3.91 (2H, q, *J* 7.1 Hz), 2.43 (3H, s), 0.89 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 3.51 minutes, 419 $(M+H)^+$.

INTERMEDIATE 34

3-[(6-Methylpyridin-2-yl)carbonyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid

From Intermediate 33 (2.30 g, 5.5 mmol) and 0.25M sodium hydroxide(aq) (17 ml, 4.3 mmol) by the method of Example 2. White solid. δ_H (DMSO-d_6) 7.89 (1H, t, *J* 7.7 Hz), 7.82-7.78 (1H, m), 7.73-7.61 (3H, m), 7.59-7.52 (3H, m), 7.46 (1H, d, *J* 7.4 Hz), 6.49 (1H, d, *J* 9.5 Hz), 2.49 (3H, s). LCMS (ES^+) RT 2.86 minutes, 391 $(M+H)^+$.

INTERMEDIATE 35

tert-Butyl {3-[(6-methylpyridin-2-yl)carbonyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl}carbamate

From Intermediate 34 (1.67 g, 4.3 mmol) and diphenylphosphoryl azide (1.3 g, 4.7 mmol) by the method of Example 3. Yellow solid (1.15 g, 58%) δ_H ($CDCl_3$) 12.35 (1H, s), 7.83-7.75 (2H, m), 7.53-7.44 (3H, m), 7.37-7.23 (3H, m), 7.26 (1H, d, *J* 9.8 Hz), 6.41 (1H, d, *J* 9.8 Hz), 2.58 (3H, s), 1.43 (9H, s). LCMS (ES^+) RT 4.00 minutes, 462 $(M+H)^+$.

INTERMEDIATE 36

3-Benzoyl-2-bromo-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

A suspension of Example 13 (2.84 g, 8.20 mmol) in acetonitrile (50 ml) at 0°C was treated with *tert*-butyl nitrite (1.50 ml, 12.3 mmol). The suspension was diluted with a mixture of acetonitrile and THF (40 ml, 1:1 mixture) and was stirred at 0°C for 10 minutes, followed by slow addition of copper(II) bromide (2.20 g, 9.84 mmol) in minimal acetonitrile. The reaction was stirred at 0°C for 5 minutes. The reaction was quenched by addition of 2M HCl(aq) (200 ml) and the aqueous extracted with DCM (2 x 200 ml). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 2-40% EtOAc in DCM) gave the *title compound* as an orange-brown solid (140 mg, 4%). δ_H ($CDCl_3$) 9.85 (2H, d, *J* 7.6 Hz), 7.36-7.62 (9H, m), 6.53 (1H, d, *J* 9.6 Hz). LCMS (ES^+) RT 3.70 minutes, 410 $^{79}Br(M+H)^+$ and 412 $^{81}Br(M+H)^+$.

EXAMPLE 1

Ethyl 3-(3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

A mixture of Intermediate 12 (5.69 g, 13 mmol) and activated manganese(IV) oxide (5.69 g of ~85%, 55 mmol) was stirred in DCM (100 ml) at r.t. for 18 h. The mixture was filtered through a short pad of Celite® and the filtrate concentrated *in vacuo*. The crude product was purified by chromatography (silica, 0-20% EtOAc in DCM) to give the *title compound* as a white solid (4.23 g, 78%). δ_H ($CDCl_3$) 7.66 (1H, s), 7.59-

7.49 (4H, m), 7.42-7.36 (4H, m), 7.31-7.27 (1H, m), 6.56 (1H, d, *J* 9.6 Hz), 4.00 (2H, q, *J* 7.1 Hz), 2.34 (3H, s), 0.92 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 3.80 minutes, 418 $(M+H)^+$.

EXAMPLE 2

3-(3-Methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid

A mixture of Example 1 (4.23 g, 10 mmol) and 0.25M NaOH(aq) (48 ml, 12 mmol) in EtOH (100 ml) was heated at reflux for 1 h. The solution was cooled to r.t. and the solvent removed *in vacuo*. The residue was dissolved in water (*ca.* 10 ml) and poured into 2M HCl(aq) (200 ml). The precipitate was filtered and dried *in vacuo* to give the *title compound* as a white solid (3.17 g, 81%). δ_H (DMSO-d_6) 7.64-7.53 (7H, m), 7.48-7.43 (2H, m), 7.39 (1H, t, *J* 7.6 Hz), 6.49 (1H, d, *J* 9.6 Hz), 2.32 (3H, s). LCMS (ES^+) RT 3.19 minutes, 390 $(M+H)^+$.

EXAMPLE 3

tert-Butyl [3-(3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]carbamate

A mixture of Example 2 (4.7 g, 12.0 mmol), diphenylphosphoryl azide (3.63 g, 13 mmol) and triethylamine (1.31 g, 13 mmol) in 2-methyl-2-propanol (100 ml) was heated at 90°C for 3 h. The reaction was cooled to r.t. and $NaHCO_3$(aq) (200 ml) added. The mixture was extracted with DCM (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (silica, 10% EtOAc in DCM) to give the *title compound* as a yellow solid (5.4 g, 90%). δ_H ($CDCl_3$) 10.6 (1H, s), 7.62-7.46 (3H, m), 7.40-7.29 (6H, m), 6.81 (1H, d, *J* 9.7 Hz), 6.36 (1H, d, *J* 9.7 Hz), 2.37 (3H, s), 1.42 (9H, s). LCMS (ES^+) RT 4.44 minutes, 461 $(M+H)^+$.

EXAMPLE 4

2-Amino-3-(3-methylbenzoyl)-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

Trifluoroacetic acid (20 ml) was added to a solution of Example 3 (5.4 g, 11.0 mmol) in DCM (20 ml) and stirred at r.t. for 5 h. $NaHCO_3$(aq) (200 ml) was added to the

reaction, and the mixture extracted with DCM (3 x 100 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (silica, 10% THF in DCM) to give the *title compound* as a yellow solid (3.0 g, 76%). δ_H ($CDCl_3$) 7.52-7.45 (3H, m), 7.33-7.30 (6H, m), 6.72 (1H, d, *J* 9.6 Hz), 6.33 (1H, d, *J* 9.6 Hz), 2.35 (3H, s). LCMS (ES^+) RT 3.11 minutes, 361 $(M+H)^+$.

EXAMPLE 5

3-(3-Methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

A mixture of Intermediate 13 (150 mg, 0.40 mmol) and manganese dioxide (300 mg, 3.4 mmol) was stirred in DCM (30 ml) at r.t. for 18 h. The solution was filtered through a short pad of Celite® and the solvent removed *in vacuo*. The crude product was purified by chromatography on silica (0-10% EtOAc in DCM) to give the *title compound* as a white solid (130 mg, 88%). δ_H ($CDCl_3$) 7.80 (1H, d, *J* 9.8 Hz), 7.76 (1H, s), 7.72-7.60 (4H, m), 7.58-7.43 (4H, m), 6.74 (1H, d, *J* 9.8 Hz), 2.48 (3H, s). LCMS (ES^+) RT 3.59 minutes, 371 $(M+H)^+$.

EXAMPLE 6

3-(3-Methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

A mixture of Example 5 (127 mg, 0.34 mmol) and 0.25M sodium hydroxide(aq) (1.36 ml, 0.34 mmol) was heated to reflux in EtOH (20 ml) for 45 minutes. The solution was cooled to room temperature, 2M HCl(aq) (100 ml) added and the aqueous extracted with DCM (2 x 100 ml). The combined DCM extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-10% EtOAc in DCM) to give the *title compound* as a white solid (125 mg, 95%). δ_H ($CDCl_3$) 7.70 (1H, br s), 7.59-7.32 (8H, m), 7.05 (1H, d, *J* 9.7 Hz), 6.44 (1H, d, *J* 9.7 Hz), 2.37 (3H, s). LCMS (ES^+) RT 3.00 minutes, 389 $(M+H)^+$.

EXAMPLE 7

2-(Azetidin-1-ylcarbonyl)-3-(3-methylbenzoyl)-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

Example 2 (300 mg, 0.77 mmol) was dissolved in DCM (10 ml). NMM (0.25 ml, 2.3 mmol), EDC (177 mg, 0.92 mmol), HOBT (124 mg, 0.92 mmol) and azetidine hydrochloride (107 mg, 1.16 mmol) were added sequentially. The solution was stirred at room temperature for 18 h before being partitioned between DCM (100 ml) and aqueous $NaHCO_3$. The aqueous layer was extracted with DCM (2 x 100 ml) and the combined organic layers were washed with 2M HCl(aq), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica (0-20% EtOAc in DCM) to give the *title compound* as a white solid (110 mg, 34%). δ_H ($CDCl_3$) 7.68 (1H, s), 7.62-7.27 (9H, m), 6.56 (1H, d, J 9.7 Hz), 3.92 (4H, br s), 2.33 (3H, s), 2.09 (2H, m). LCMS (ES^+) RT 3.28 minutes, 429 $(M+H)^+$.

EXAMPLE 8

3-(3-Methylbenzoyl)-7-phenyl-2-(piperidin-1-yl)thieno[2,3-*b*]pyridin-6(7*H*)-one

Intermediate 14 (100 mg of 75% pure material, 18 mmol) was dissolved in toluene (5 ml). Cs_2CO_3 (108 mg, 0.33 mmol), tris(dibenzylideneacetone)dipalladium(0) (11 mg, 0.012 mmol), BINAP (15 mg, 0.024 mmol) and piperidine (0.029 ml, 0.29 mmol) were added sequentially. The mixture was heated at reflux for 18 h, cooled to room temperature and poured into water (100 ml). The aqueous mixture was extracted with DCM (2 x 100 ml), the combined organic extracts dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by chromatography on silica (5-20% EtOAc in DCM) to give the *title compound* as a yellow solid (22 mg, 29%). δ_H (DMSO-d_6) 7.87 (1H, d, *J* 9.6 Hz), 7.67-7.32 (9H, m), 6.53 (1H, d, *J* 9.6 Hz), 2.74 (4H, m), 2.37 (3H, s), 1.25-0.96 (6H, m). LCMS (ES^+) RT 4.30 minutes, 429 $(M+H)^+$.

EXAMPLE 9

3-(3-Methylbenzoyl)-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

Example 2 (100 mg, 0.26 mmol) was dissolved in 1,4-dioxane (5 ml) and HCl (conc.) (1 ml) added. The solution was heated in a microwave (180°C, 200 psi) for 5 minutes. The cooled solution was poured into DCM (100 ml) and washed with aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a crude product which was purified by chromatography on silica (0-20% EtOAc in DCM)

to give the *title compound* as a white solid (12 mg, 12%). δ_H (DMSO-d_6) 8.25 (1H, d, *J* 9.6 Hz), 7.73 (1H, s), 7.63-7.38 (9H, m), 6.57 (1H, d, *J* 9.6 Hz), 2.34 (3H, s). LCMS (ES^+) RT 3.65 minutes, 346 $(M+H)^+$.

EXAMPLE 10

Ethyl 3-benzoyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

From Intermediate 15 by the method of Example 1. White solid. δ_H ($CDCl_3$) 7.84-7.78 (2H, m), 7.59-7.51 (4H, m), 7.44-7.37 (5H, m), 6.56 (1H, d, *J* 9.6 Hz), 3.99 (2H, q, *J* 7.1 Hz), 0.90 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 3.62 minutes, 404 $(M+H)^+$.

EXAMPLE 11

3-Benzoyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid

A mixture of Example 10 (3.0 g, 7.4 mmol) and 0.25M sodium hydroxide(aq) (29 ml, 7.4 mmol) was stirred in EtOH (150 ml) and heated at reflux for 1 h. The solution was cooled to r.t. and the solvent removed *in vacuo*. The residue was dissolved in water (*ca.* 10 ml) and poured into 2M HCl(aq) (200 ml). The precipitate was filtered and dried *in vacuo* to give the *title compound* as a white solid (1.89 g, 68%). δ_H (DMSO-d_6) 7.91-7.89 (2H, m), 7.79-7.58 (9H, m), 6.60 (1H, d, *J* 9.6 Hz). LCMS (ES^+) RT 3.06 minutes, 376 $(M+H)^+$.

EXAMPLE 12

tert-Butyl (3-benzoyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)carbamate

From Example 11 (1.46 g, 3.9 mmol), diphenylphosphoryl azide (1.17 g, 4.3 mmol) and triethylamine (0.43 g, 4.3 mmol) in 2-methyl-2-propanol (30 ml), by the method of Example 3, to give the *title compound* as a yellow solid (1.5 g, 84%). δ_H ($CDCl_3$) 10.66 (1H, s), 7.60-7.43 (8H, m), 7.33 (2H, d, *J* 7.4 Hz), 6.80 (1H, d, *J* 9.7 Hz), 6.36 (1H, d, *J* 9.7 Hz), 1.42 (9H, s). LCMS (ES^+) RT 4.07 minutes, 447 $(M+H)^+$.

EXAMPLE 13

2-Amino-3-benzoyl-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

From Example 12 by the method of Example 4. Yellow solid. δ_H (DMSO-d_6) 8.29 (2H, br s), 7.70-7.50 (10H, m), 6.60 (1H, d, *J* 9.6 Hz), 6.23 (1H, d, *J* 9.6 Hz). LCMS (ES^+) RT 3.016 minutes, 347 $(M+H)^+$.

EXAMPLE 14

N-(3-Benzoyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)acetamide

To a solution of Example 13 (270 mg, 0.78 mmol) in DMF (10 ml) 4-dimethylaminopyridine (~10 mg, catalytic) was added. Acetic acid (0.074 ml, 0.78 mmol) premixed in DMF (~1 ml) was added to the reaction mixture and stirred at r.t. for 18 h. $NaHCO_3$(aq) (20 ml) was added, and the mixture was extracted with DCM (2 x 20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (silica, 20-40% EtOAc in DCM), to give the *title compound* as a yellow solid (123 mg, 41%). δ_H (DMSO-d_6) 10.98 (1H, s), 7.78-7.75 (2H, m), 7.70-7.50 (8H, m) 7.17 (1H, d, *J* 9.6 Hz), 6.40 (1H, d, *J* 9.6 Hz), 2.02 (3H, s). LCMS (ES^+) RT 3.26 minutes, 389 $(M+H)^+$.

EXAMPLE 15

N-[3-(3-Methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]acetamide

From Example 4 by the method of Example 14. Yellow solid. δ_H (DMSO-d_6) 11.03 (1H, br s), 7.76-7.48 (9H, m), 7.24 (1H, d, *J* 9.7 Hz), 6.47 (1H, d, *J* 9.7 Hz), 2.46 (3H, s), 2.10 (3H, s). LCMS (ES^+) RT 3.42 minutes, 403 $(M+H)^+$.

EXAMPLE 16

N-(3-Benzoyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)methanesulfonamide

Trifluoroacetic acid (5 ml) was added to a solution of Intermediate 16 (100 mg, 1.90 mmol) in DCM (5 ml) and stirred at r.t. for 5 h. $NaHCO_3$(aq) (50 ml) was added to the reaction, and the mixture was extracted with DCM (3 x 10 ml). The combined

organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (silica, 20% THF in DCM) to give the *title compound* as a yellow solid (11 mg, 14%). δ_H ($CDCl_3$) 10.12 (1H, s), 7.67-7.45 (8H, m), 7.33 (2H, d, *J* 7.8 Hz), 6.89 (1H, d, *J* 9.7 Hz), 6.42 (1H, d, *J* 9.7 Hz), 2.99 (3H, s). LCMS (ES^+) RT 3.11 minutes, 425 $(M+H)^+$.

EXAMPLE 17

N-[3-(3-Methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]methanesulfonamide

From Intermediate 17 by the method of Example 16. Yellow solid. δ_H ($CDCl_3$) 10.07 (1H, s), 7.56-7.32 (9H, m), 6.89 (1H, d, *J* 9.7 Hz), 6.36 (1H, d, *J* 9.7 Hz), 2.99 (3H, s), 2.38 (3H, s). LCMS (ES^+) RT 3.22 minutes, 439 $(M+H)^+$.

EXAMPLE 18

2-(Azetidin-1-yl)-3-(3-methylbenzoyl)-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

From Intermediate 14 and azetidine by the method of Example 8. Yellow solid. δ_H ($CDCl_3$) 7.58-7.44 (5H, m), 7.39-7.23 (5H, m), 6.39 (1H, d, *J* 9.7 Hz), 3.66 (4H, t, *J* 7.4 Hz), 2.35 (3H, s), 2.22 (2H, m). LCMS (ES^+) RT 3.55 minutes, 401 $(M+H)^+$.

EXAMPLE 19

N-(3-Benzoyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)piperidine-4-carboxamide

Example 13 (500 mg, 1.45 mmol) was dissolved in DCM (10 ml). NMM (1.0 ml, 8.7 mmol), HOBT (470 mg, 3.4 mmol), EDC (670 mg, 3.4 mmol) and BOC-isonipecotic acid (740 mg, 3.4 mmol) were added sequentially. The solution was heated at reflux for 48 h, cooled to room temperature and poured into DCM (250 ml). The aqueous was sequentially washed with $NaHCO_3$ (sat. aq) (100 ml) and cold 2M HCl(aq) (100 ml). The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by chromatography on silica (10-30% EtOAc in DCM) to give a yellow solid (350 mg, 42%). This intermediate was dissolved in DCM (20 ml) and TFA (10 ml)

was added. The reaction was stirred at room temperature for 20 h before being poured into cold $NaHCO_3$ (sat. aq) (500 ml) (CAUTION). The product was extracted with DCM (2 x 250 ml), the combined organic layers dried ($MgSO_4$) and the solvent removed *in vacuo* to give the *title compound* as a yellow solid (262 mg, 94%). δ_H (DMSO-d_6) 7.61-7.33 (12H, m), 7.28 (1H, d), 2.87 (2H, m), 2.54 (2H, t, *J* 10.5 Hz), 2.23 (1H, m), 1.45 (2H, m), 1.30 (2H, m). LCMS (ES^+) RT 2.27 minutes, 458 $(M+H)^+$.

EXAMPLE 20

N'-(3-Benzoyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl)-*N,N*-dimethylurea

A solution of phosgene (0.188 ml, 0.32 mmol) in DCM (10 ml) was cooled to -30°C under nitrogen. Triethylamine (0.088 ml, 0.64 mmol) and Example 13 (100 mg, 0.29 mmol) were added, and the reaction mixture stirred at -30°C for 0.5 h. Dimethylamine (0.29 ml of a 2.0M solution in THF, 0.58 mmol) was added and the mixture was warmed to r.t. and stirred for 18 h. Water (10 ml) was added, and the mixture was extracted with DCM (2 x 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography (silica, 5% THF in DCM) to give the *title compound* as a yellow solid (55 mg, 46%). δ_H ($CDCl_3$) 11.95 (1H, s), 7.82-7.43 (8H, m), 7.37-7.31 (2H,m), 6.79 (1H, d, *J* 9.7 Hz), 6.38 (1H, d, *J* 9.7 Hz), 3.02 (6H, s). LCMS (ES^+) RT 3.36 minutes, 418 $(M+H)^+$.

EXAMPLE 21

N-(2-Hydroxy-2-methylpropyl)-*N'*-[3-(3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]urea

From Example 4 and 1-amino-2-methylpropan-2-ol hydrochloride (137 mg, 1.1 mmol), by the method of Example 20, to give the *title compound* as a yellow solid (174 mg, 66%). δ_H ($CDCl_3$) 11.22 (1H, s), 7.51-7.42 (3H, m), 7.35-7.29 (6H, m), 6.73 (1H, d, *J* 9.7 Hz), 6.31 (1H, d, *J* 9.7 Hz), 5.82 (1H, br s), 3.15 (2H, d, *J* 5.9 Hz), 2.34 (3H, s), 1.14 (6H, s), 0.80-0.75 (1H,m). LCMS (ES^+) RT 3.12 minutes, 476 $(M+H)^+$.

EXAMPLE 22

4-Methyl-*N*-[3-(3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]piperazine-1-carboxamide

From Example 4 and 1-methylpiperazine (0.12 ml, 1.1 mmol), by the method of Example 20, to give the *title compound* as a yellow solid (238mg, 88%). δ_H ($CDCl_3$) 12.34 (1H, s), 7.69-7.60 (3H, m), 7.55-7.47 (6H, m), 6.97 (1H, d, *J* 9.7 Hz), 6.48 (1H, d, *J* 9.7 Hz), 4.28 (2H, m), 4.05 (2H, m), 3.60 (2H, m), 2.89 (5H, s), 2.53 (3H, s). LCMS (ES^+) RT 2.28 minutes, 487 $(M+H)^+$.

EXAMPLE 23

N-[3-(3-Methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]urea

From Example 4 and ammonia(aq) (0.07 ml, 4.1 mmol), by the method of Example 20, to give the *title compound* as a yellow solid (80 mg, 36%). δ_H ($CDCl_3$) 10.58 (1H, s), 7.59-7.50 (3H, m), 7.42-7.37 (6H, m), 7.10 (1H, br s), 6.67 (1H, d, *J* 9.7 Hz), 6.19 (1H, d, *J* 9.7 Hz), 2.33 (3H, s). LCMS (ES^+) RT 3.01 minutes, 404 $(M+H)^+$.

EXAMPLE 24

N,*N*-Dimethyl-*N'*-[3-(3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]urea

From Example 4 and dimethylamine (0.55 ml of a 2.0M solution in THF, 1.1 mmol), by the method of Example 20, to give the *title compound* as a yellow solid (59 mg, 25%). δ_H ($CDCl_3$) 11.94 (1H, s), 7.52-7.45 (3H, m), 7.38-7.32 (6H, m), 6.80 (1H, d, *J* 9.7 Hz), 6.30 (1H, d, *J* 9.7 Hz), 3.02 (6H, s), 2.33 (3H, s). LCMS (ES^+) RT 3.51 minutes, 432 $(M+H)^+$.

EXAMPLE 25

N-[3-(3-Methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]azetidine-1-carboxamide

From Example 4 and azetidine hydrochloride (102 mg, 1.1 mmol), by the method of Example 20, to give the *title compound* as a yellow solid (157 mg, 64%). δ_H ($CDCl_3$) 11.24 (1H, s), 7.52-7.42 (3H, m), 7.37-7.30 (6H, m), 6.78 (1H, d, *J* 9.7 Hz), 6.29 (1H, d, *J* 9.7 Hz), 4.09 (4H, t, *J* 7.6 Hz), 2.36-2.27 (5H, m). LCMS (ES^+) RT 3.52 minutes, 444 $(M+H)^+$.

EXAMPLE 26

N-Allyl-*N'*-[3-(3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]urea

From Example 4 and allylamine (0.08 ml, 1.1 mmol), by the method of Example 20, to give the *title compound* as a yellow solid (120 mg, 49%). δ_H ($CDCl_3$) 11.32 (1H, s), 7.52-7.42 (3H, m), 7.36-7.29 (6H, m), 6.73 (1H, d, *J* 9.7 Hz), 6.30 (1H, d, *J* 9.7 Hz), 5.80-5.71 (1H, m), 5.21-5.08 (3H, m), 3.79 (2H, t, *J* 5.7 Hz), 2.36 (3H, s). LCMS (ES^+) RT 3.49 minutes, 444 $(M+H)^+$.

EXAMPLE 27

(2*R*)-2-(Hydroxymethyl)-*N*-[3-(3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]pyrrolidine-1-carboxamide

From Example 4 and (*R*)-(-)-2-pyrrolidinemethanol (0.11 ml, 1.1 mmol), by the method of Example 20, to give the *title compound* as a yellow solid (89 mg, 33%). δ_H ($CDCl_3$) 11.73 (1H, s), 7.53-7.44 (3H, m), 7.38-7.32 (6H, m), 6.80 (1H, d, *J* 9.7 Hz), 6.30 (1H, d, *J* 9.7 Hz), 4.05 (1H, br s), 3.66-3.54 (4H, m), 2.37 (3H, s), 2.04-1.91 (3H,m), 1.81-1.78 (1H, m), 1.18 (1H, s). LCMS (ES^+) RT 3.31 minutes, 488 $(M+H)^+$.

EXAMPLE 28

N-(1-Ethylpyrrolidin-3-yl)-*N'*-[3-(3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]urea

To a solution of Intermediate 18 (258 mg, 0.43 mmol) in EtOH (20 ml) palladium (4.5 mg, 10 wt % on carbon powder, 0.043 mmol) was added. The reaction was placed under an atmosphere of nitrogen and stirred at r.t. for 18 h. The solution was filtered through a short pad of Celite® and the solvent removed *in vacuo*. The crude product was purified by preparative HPLC to give the *title compound* as a yellow solid (6.8 mg, 3%). δ_H (DMSO-d_6) 10.72 (1H, s), 8.29 (1H, d, *J* 5.8 Hz), 7.87-7.58 (3H, m), 7.50-7.41 (6H, m), 6.73 (1H, d, *J* 9.7 Hz), 6.27 (1H, d, *J* 9.7 Hz), 4.08 (1H, br s), 2.87 (2H, br s) 2.67-2.62 (4H, m), 2.40 (3H, s), 2.17-2.13 (1H, m), 1.64-1.59 (1H, m), 1.07 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 2.33 minutes, 501 $(M+H)^+$.

EXAMPLE 29

N-[3-(3-Methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]-2-(methylsulfonyl)hydrazinecarboxamide

From Example 4 and methanesulfonyl hydrazine (121 mg, 1.1 mmol), by the method of Example 20, to give the *title compound* as a yellow solid (10 mg, 4%). δ_H (DMSO-d_6) 9.98 (1H, br s), 9.77 (1H, br s), 7.78-7.70 (3H, m), 7.61-7.54 (6H, m), 6.90 (1H, d, *J* 9.7 Hz), 6.41 (1H, d, *J* 9.7 Hz), 3.11 (3H, br s), 2.50 (3H, s). LCMS (ES^+) RT 3.00 minutes, 497 $(M+H)^+$.

EXAMPLE 30

3-Benzoyl-*N*-methyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

From Example 11 with methylamine hydrochloride, by the method of Example 7. White solid. δ_H ($CDCl_3$) 7.82 (2H, m), 7.70-7.19 (8H, m), 7.02 (1H, d, *J* 9.7 Hz), 6.41 (1H, d, *J* 9.7 Hz), 2.76 (3H, d, *J* 4.8 Hz). LCMS (ES^+) RT 3.07 minutes, 389 $(M+H)^+$.

EXAMPLE 31

2-(Azetidin-1-ylcarbonyl)-3-benzoyl-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

From Example 11 with azetidine hydrochloride, by the method of Example 7. White solid. δ_H (DMSO-d_6) 7.54 (2H, m), 7.66-7.46 (9H, m), 6.50 (1H, d, *J* 9.8 Hz), 3.90 (4H, br s), 2.44 (2H, m). LCMS (ES^+) RT 3.14 minutes, 415 $(M+H)^+$.

EXAMPLE 32

3-Benzoyl-*N*-(1,1-dimethyl-2-hydroxyethyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

From Example 11 with 1,1-dimethyl-2-hydroxyethylamine, by the method of Example 7. White solid. δ_H ($CDCl_3$) 7.81 (2H, m), 7.64-7.34 (8H, m), 7.10 (1H, d, *J* 9.7 Hz), 6.25 (1H, d, *J* 9.7 Hz), 3.44 (2H, s), 1.14 (6H, s). LCMS (ES^+) RT 3.13 minutes, 447 $(M+H)^+$.

EXAMPLE 33

3-Benzoyl-*N*,*N*-dimethyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

From Example 11 with dimethylamine, by the method of Example 7. White solid. δ_H ($CDCl_3$) 7.84-7.76 (2H, m), 7.57-7.35 (9H, m), 6.63 (1H, d, *J* 9.7 Hz), 2.58 (6H, s). LCMS (ES^+) RT 3.11 minutes, 403 $(M+H)^+$.

EXAMPLE 34

3-Benzoyl-2-{[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl}-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

From Example 11 with (*S*)-prolinol, by the method of Example 7. White solid. δ_H (DMSO-d_6) 7.83-7.52 (11H, m), 6.63 (1H, d, *J* 9.7 Hz), 3.70 (1H, m), 3.40-3.29 (2H, m), 3.09 (1H, m), 2.78 (1H, m), 1.75 (4H, m). LCMS (ES^+) RT 2.96 minutes, 459 $(M+H)^+$.

EXAMPLE 35

3-Benzoyl-2-(morpholin-4-ylcarbonyl)-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

From Example 11 with morpholine, by the method of Example 7. White solid. δ_H ($CDCl_3$) 7.82 (2H, m), 7.58 (1H, d, *J* 9.7 Hz), 7.46-7.15 (8H, m), 6.51 (1H, d, *J* 9.7 Hz), 3.22 (4H, m), 3.01 (4H, m). LCMS (ES^+) RT 3.09 minutes, 445 $(M+H)^+$.

EXAMPLE 36

3-Benzoyl-7-phenyl-2-(pyrrolidin-1-ylcarbonyl)thieno[2,3-*b*]pyridin-6(7*H*)-one

From Example 11 with pyrrolidine, by the method of Example 7. White solid. δ_H ($CDCl_3$) 7.82 (2H, m), 7.74 (1H, d, *J* 9.7 Hz), 7.59-7.37 (8H, m), 6.61 (1H, d, *J* 9.7 Hz), 3.10 (4H, br s), 1.63 (4H, br s). LCMS (ES^+) RT 3.22 minutes, 429 $(M+H)^+$.

EXAMPLE 37

3-Benzoyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 19 by the method of Example 5. White solid. δ_H ($CDCl_3$) 7.83 (2H, m), 7.70 (1H, d, *J* 9.7 Hz), 7.67-7.48 (6H, m), 7.36 (2H, m), 6.64 (1H, d, *J* 9.7 Hz). LCMS (ES^+) RT 3.43 minutes, 357 $(M+H)^+$.

EXAMPLE 38

3-Benzoyl-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

From Example 37 by the method of Example 6. White solid. δ_H ($CDCl_3$) 7.80 (2H, m), 7.67-7.35 (8H, m), 7.04 (1H, d, *J* 9.7 Hz), 6.45 (1H, d, *J* 9.7 Hz). LCMS (ES^+) RT 2.86 minutes, 375$(M+H)^+$.

EXAMPLE 39

Ethyl 3-benzoyl-7-(cyclopropylmethyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

From Intermediate 20 by the method of Example 1. White solid. δ_H (DMSO-d_6) 7.88 (2H, m), 7.76 (1H, tt, *J* 1.2, 6.2 Hz), 7.61 (2H, m), 7.54 (1H, d, *J* 9.5 Hz), 6.55 (1H, d, *J* 9.5 Hz), 4.12 (4H, m), 1.43 (1H, m), 1.02 (3H, t, *J* 7.1 Hz), 0.60 (4H, m). LCMS (ES^+) RT 3.71 minutes, 382 $(M+H)^+$.

EXAMPLE 40

2-Amino-3-benzoyl-7-(cyclopropylmethyl)thieno[2,3-*b*]pyridin-6(7*H*)-one

From Example 39 by the method of Examples 2, 3 and 4 (intermediates taken on without purification). Yellow solid. δ_H (DMSO-d_6) 8.36 (2H, m), 7.65-7.48 (5H, m), 6.48 (1H, d, *J* 9.6 Hz), 6.30 (1H, d, *J* 9.6 Hz), 3.90 (2H, d, *J* 7.0 Hz), 1.30-1.21 (1H, m), 0.55-0.44 (4H, m). LCMS (ES^+) RT 2.93 minutes, 325 $(M+H)^+$.

EXAMPLE 41

3-Benzoyl-7-(2-chlorophenyl)-6-oxo-6,7-dihydrothieno[2,3-*b*]pyridine-2-carbonitrile

From Intermediate 21 (333 mg, 0.93 mmol) and manganese(IV) oxide (333 mg, 3.3 mmol) by the method of Example 5. White solid (102 mg, 30%). δ_H ($CDCl_3$) 7.86-7.84 (2H, m), 7.74 (1H, d, *J* 9.8 Hz), 7.67-7.63 (2H, m), 7.54-7.46 (4H, m), 7.41-7.38 (1H, m), 6.65 (1H, d, *J* 9.8 Hz). LCMS (ES^+) RT 3.57 minutes, 391 $(M+H)^+$.

EXAMPLE 42

2-Amino-3-benzoyl-7-(2-chlorophenyl)thieno[2,3-*b*]pyridin-6(7*H*)-one

Example 41 (91 mg, 0.23 mmol) was suspended in EtOH (10 ml), 0.25M NaOH (1.8 ml) added and the solution heated to reflux for 60 h. The reaction was cooled to room temperature and the solvent removed *in vacuo*. The solid residue was taken up in water (10 ml) and poured into 2M HCl (50 ml). The precipitate formed was filtered and dried *in vacuo* to give a white solid (35 mg, 37%). This crude intermediate was converted to the *title compound* by the methods of Examples 3 and 4. Yellow solid. δ_H (DMSO-d_6) 8.30 (2H, m), 7.83 (1H, dd, *J* 1.8, 7.1 Hz), 7.72-7.53 (8H, m), 6.62 (1H, d, *J* 9.7 Hz), 6.24 (1H, d, *J* 9.7 Hz). LCMS (ES^+) RT 3.18 minutes, 381 $(M+H)^+$.

EXAMPLE 43

3-(3-Chlorobenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

From Intermediate 23 (53 mg, 0.136 mmol) and 0.25M sodium hydroxide(aq) (0.27 ml, 0.07 mmol) by the method of Example 6. White solid (20 mg, 36%). δ_H (DMSO-d_6) 8.43 (2H, s), 7.70-7.66 (6H, m), 7.63-7.56 (4H, m), 6.55 (1H, d, *J* 9.6 Hz). LCMS (ES^+) RT 3.08 minutes, 409 $(M+H)^+$.

EXAMPLE 44

Ethyl 3-(3-chlorobenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

From Intermediate 24 by the method of Example 1. White solid. δ_H (DMSO-d_6) 7.79 (1H, d, *J* 1.8 Hz), 7.73-7.68 (2H, m), 7.64-7.50 (7H, m), 6.50 (1H, d, *J* 9.7 Hz), 3.95 (2H, q, *J* 7.1 Hz), 0.87 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 3.82 minutes, 438 $(M+H)^+$.

EXAMPLE 45

2-Amino-3-(3-chlorobenzoyl)-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

From Example 44 by the methods of Examples 2, 3 and 4 (intermediates used crude). Yellow solid. δ_H (DMSO-d_6) 8.46 (2H, m), 7.83-7.59 (9H, m), 6.76 (1H, d, *J* 9.7 Hz), 6.37 (1H, d, *J* 9.7 Hz). LCMS (ES^+) RT 3.21 minutes, 381 $(M+H)^+$.

EXAMPLE 46

N-[3-(3-Chlorobenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl]acetamide

From Example 45 by the method of Example 14. Yellow solid. δ_H (DMSO-d_6) 13.70 (1H, s), 7.70-7.41 (9H, m), 7.21 (1H, d, *J* 9.6 Hz), 6.36 (1H, d, *J* 9.6 Hz), 1.94 (3H, s). MS (ES^+) RT 3.42 minutes, 423 $(M+H)^+$.

EXAMPLE 47

3-(2,4-Difluorobenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

From Intermediate 26 (14 mg, 0.036 mmol) and 0.25M sodium hydroxide(aq) (0.07 ml, 0.02 mmol) by the method of Example 6. White solid (6 mg, 41%). δ_H (DMSO-d_6) 8.51 (2H, s), 7.82-7.76 (1H, m), 7.70-7.52 (6H, m), 7.40-7.34 (1H, m), 7.22 (1H, dt, *J* 2.2, 8.4 Hz), 6.57 (1H, d, *J* 9.6 Hz). LCMS (ES^+) RT 2.94 minutes, 411 $(M+H)^+$.

EXAMPLE 48

3-(4-Fluoro-3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

From Intermediate 28 (89 mg, 0.23 mmol) and 0.25M sodium hydroxide(aq) (0.44 ml, 0.11mmol) by the method of Example 6. White solid (28 mg, 30%). δ_H ($CDCl_3$) 7.84 (1H, dd, *J* 1.7, 7.4 Hz), 7.76-7.65 (6H, m), 7.58 (1H, d, *J* 9.6 Hz), 7.34 (1H, t, *J* 9.0 Hz), 6.59 (1H, d, *J* 9.6 Hz), 2.35 (3H, s). LCMS (ES^+) RT 3.08 minutes, 407 $(M+H)^+$.

EXAMPLE 49

Ethyl 3-(4-fluoro-3-methylbenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylate

From Intermediate 29 by the method of Example 1. White solid. δ_H (DMSO-d_6) 7.80 (1H, dd, *J* 1.7, 7.3 Hz), 7.67-7.52 (7H, m), 7.27 (1H, t, *J* 8.9 Hz), 6.51 (1H, d, *J* 9.7 Hz), 3.97 (2H, q, *J* 7.1 Hz), 2.24 (3H, s), 0.90 (3H, t, *J* 7.1 Hz). LCMS (ES^+) RT 3.77 minutes, 436 $(M+H)^+$.

EXAMPLE 50

2-Amino-3-(4-fluoro-3-methylbenzoyl)-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

From Example 49 by the methods of Examples 2, 3 and 4. Obtained as a 1:1 mixture with Example 51. Purification by preparative HPLC gave the *title compound* as a

yellow solid. δ_H (DMSO-d_6) 8.37 (2H, m), 7.89-7.62 (7H, m), 7.51 (1H, m), 6.94 (1H, d, *J* 9.7 Hz), 6.47 (1H, d, *J* 9.7 Hz), 2.74 (3H, s). LCMS (ES^+) RT 3.17 minutes, 379 $(M+H)^+$.

EXAMPLE 51

2-Amino-3-(4-ethoxy-3-methylbenzoyl)-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

From Example 49 by the methods of Examples 2, 3 and 4. Obtained as a 1:1 mixture with Example 50. Purification by preparative HPLC gave the *title compound* as a tan solid. δ_H (DMSO-d_6) 7.63 (2H, m), 7.43-7.14 (7H, m), 6.79 (1H, m), 6.62 (1H, d, *J* 9.7 Hz), 6.00 (1H, d, *J* 9.7 Hz), 3.89 (2H, q, *J* 6.9 Hz), 1.97 (3H, s), 1.16 (3H, t, *J* 6.9 Hz). LCMS (ES^+) RT 3.38 minutes, 405 $(M+H)^+$.

EXAMPLE 52

3-(3-Chloro-4-fluorobenzoyl)-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridine-2-carboxamide

From Intermediate 31 (22 mg, 0.054 mmol) and 0.25M sodium hydroxide(aq) (0.11 ml, 0.27 mmol) by the method of Example 6. White solid (4 mg, 17%). δ_H (DMSO-d_6) 8.50 (2H, s), 7.94 (1H, dd, *J* 2.0, 7.1 Hz), 7.79-7.50 (8H, m), 6.54 (1H, d, *J* 9.6 Hz). LCMS (ES^+) RT 3.12 minutes, 427 $(M+H)^+$.

EXAMPLE 53

2-Amino-3-[(6-methylpyridin-2-yl)carbonyl]-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

From Intermediate 35 (1.15 g, 2.5 mmol) and trifluoroacetic acid (5 ml), by the method of Example 4, to give the *title compound* as a yellow solid (646 mg, 72%). δ_H ($CDCl_3$) 7.75 (1H, t, *J* 7.7 Hz), 7.56-7.51 (1H, m), 7.50-7.42 (3H, m) 7.31-7.28 (3H, m), 7.01 (2H, s), 6.67 (1H, d, *J* 9.7 Hz), 6.27 (1H, d, *J* 9.7 Hz), 2.53 (3H, s). LCMS (ES^+) RT 3.69 minutes, 362 $(M+H)^+$.

EXAMPLE 54

N-{3-[(6-Methylpyridin-2-yl)carbonyl]-6-oxo-7-phenyl-6,7-dihydrothieno[2,3-*b*]pyridin-2-yl}acetamide

From Example 53 (100 mg, 0.27 mmol) and acetic anhydride (0.026 ml, 0.27 mmol) by the method of Example 14. Yellow solid (66 mg, 60%). δ_H ($CDCl_3$) 12.11 (1H, s), 7.81 (1H, t, *J* 7.7 Hz), 7.67 (1H, d, *J* 7.7 Hz), 7.54-7.45 (3H, m), 7.37-7.31 (3H, m), 6.85 (1H, d, *J* 9.7 Hz), 6.37 (1H, d, *J* 9.7 Hz), 2.55 (3H, s), 2.21 (3H, s). LCMS (ES^+) RT 3.07 minutes, 404 $(M+H)^+$.

EXAMPLE 55

3-Benzoyl-2-(dimethylamino)-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

A mixture of Intermediate 36 (125 mg, 0.31 mmol), dimethylamine hydrochloride (30 mg, 0.37 mmol), cesium carbonate (303 mg, 0.93 mmol) and BINAP (41 mg, 0.06 mmol) in toluene (4 ml) in a Schlenk tube was degassed and tris(dibenzylideneacetone)-dipalladium(0) (29 mg, 0.03 mmol) added. The mixture was heated at 100°C overnight. The reaction was diluted with DCM (50 ml) and washed with 2M HCl(aq) (200 ml). The organic phase was collected, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (silica, 20% EtOAc in DCM) gave the *title compound* as a yellow-brown solid (45 mg, 39%). δ_H (DMSO-d_6) 7.99 (2H, dd, *J* 8.6, 1.6 Hz), 7.70-7.88 (9H, m), 6.64 (1H, d, *J* 9.6 Hz), 2.79 (6H, s). LCMS (ES^+) RT 3.40 minutes, 375 $(M+H)^+$.

EXAMPLE 56

3-Benzoyl-7-phenylthieno[2,3-*b*]pyridin-6(7*H*)-one

From Example 11 by the method of Example 9. Pink solid. δ_H ($CDCl_3$) 8.43 (1H, d, *J* 9.6 Hz), 7.75-7.76 (2H, m), 7.38-7.62 (9H, m), 6.63 (1H, d, *J* 9.6 Hz). LCMS (ES^+) RT 3.44 minutes, 332 $(M+H)^+$.

BIOLOGICAL ASSAYS

The following assays and animal models can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each assay an IC_{50} value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition.

Preparation of activated human p38α for inhibitor assays

Purification of human p38α

Human p38α, incorporating an *N*-terminal (His)6 tag, was expressed in baculovirus-infected High-Five™ cells (Invitrogen) according to the manufacturer's instructions. The cells were harvested 72 h post-infection and lysed in phosphate-buffered saline (PBS) containing 1% (w/v) β-octylglucoside and Complete, EDTA-free™ protease inhibitors (Roche Molecular Biochemicals). The lysate was centrifuged at 35000 x g for 30 min at 4°C and the supernatant applied to a NiNTA™ column (Qiagen). Bound protein was eluted by 150 mM imidazole in PBS (after a wash with 15 mM imidazole in PBS) and directly applied to a HiTrap Q™ column (AP Biotech). Bound protein was eluted using a 20 column volume, 0 to 1 M NaCl gradient. Fractions containing (His)6-p38 were aliquoted and stored at -70°C prior to their activation.

Preparation of GST-MKK6EE-containing lysates

E. coli (BL21 pLysS) expressing the constitutively-activated form of human MKK6 fused with an *N*-terminal glutathione-*S*-transferase tag (GST-MKK6EE) were harvested by centrifugation and frozen at -70°C. Cells were lysed by resuspension in 1/10th the culture volume of PBS containing Complete, EDTA-free™ protease inhibitors followed by sonication on ice for 4 x 15 sec. Cell debris was removed by centrifugation at 35,000 x g and the resultant supernatant stored in aliquots at -70°C.

Activation of (His)6-p38

0.45 ml of purified (His)6-p38 was incubated with 50 µl of the GST-MKK6EE-containing lysate for 30 min at 23°C in the presence of 1 mM β-glycerophosphate, 10 mM $MgCl_2$ and 9 mM ATP. The extent of activation was monitored by mass spectrometric detection of the doubly-phosphorylated form of (His)6-p38, which routinely comprised

greater than 90% of the final (His)6-p38 preparation. The activated (His)6-p38 was then diluted x 10 in PBS and repurified using the method described above. The concentration of purified, activated (His)6-p38 was measured by UV absorbance at 280 nm using A280, 0.1% = 1.2 and the preparation stored in aliquots at -70°C prior to its use in inhibitor assays.

p38 Inhibition Assays

Inhibition of phosphorylation of biotinylated myelin basic protein (MBP)

The inhibition of p38-catalysed phosphorylation of biotinylated MBP is measured using a DELFIA-based format. The assay was performed in a buffer comprising 20 mM HEPES (pH 7.4), 5 mM $MgCl_2$ and 3 mM DTT. For a typical IC_{50} determination, biotinylated MBP (2.5 μM) was incubated at room temperature in a streptavidin-coated microtitre plate together with activated gst-p38 (10 nM) and ATP (1 μM) in the presence of a range of inhibitor concentrations (final concentration of DMSO is 2 percent). After fifteen minutes the reaction was terminated by the addition of EDTA (75 mM). The microtitre plate was then washed with Tris-buffered saline (TBS), prior to the addition of 100 μl of anti-phospho MBP antibody (mouse) together with europium-labeled anti-mouse IgG antibody. After one hour at room temperature the plate was again washed in TBS followed by the addition of Enhancement solution (PerkinElmer Wallac). Fluorescence measurements were performed after a further fifteen minutes at room temperature. IC_{50} values are determined from the plot of $\log_{10}$[inhibitor concentration] (x-axis) versus percentage inhibition of the fluorescence generated by a control sample in the absence of inhibitor (y-axis).

Purification of human Peripheral Blood Mononuclear Cells

Peripheral blood mononuclear cells (PBMC) were isolated from normal healthy volunteers. Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), diluted 1 in 4 in RPMI 1640 (Gibco, UK) and centrifuged at 400 x g for 35 min over a Ficoll-paque gradient (Amersham-Pharmacia Biotech, UK). Cells at the interface were removed and washed once followed by a low speed spin (250 x g) to remove platelets. Cells were then resuspended in DMEM containing 10% FCS, penicillin 100 units ml^{-1}, streptomycin 50 μg ml^{-1} and glutamine 2 mM (Gibco, UK).

Inhibitor dilutions

Inhibitor stocks (20 mM) were kept as a frozen solution (-20°C) in DMSO. Serial dilutions of inhibitors were performed in DMSO as 250-times concentrated stocks. Inhibitors were diluted 1 in 250 into tissue culture media, prewarmed to 37°C and transferred to plates containing PBMC. PBMC and inhibitors were incubated together for 30 min prior to addition of LPS. Inhibitors used in whole blood assays were prepared according to a different regime. Using the same stock solution serial dilutions of inhibitors were performed in DMSO. Inhibitors were then diluted 1 in 500 straight into whole blood in a volume of 1 µl. Inhibitor was incubated with whole blood for 30 min prior to the addition of LPS.

LPS stimulation of PBMC

PBMC were resuspended at a density of 2×10^5 cells/well in flat-bottomed 96-well tissue culture treated plates. After the addition of inhibitor cells were stimulated with an optimal dose of LPS (*E. coli* strain B5:055, Sigma, at a final concentration of 1 $\mu g ml^{-1}$) and incubated at 37°C in 5% CO_2/95% air for 18 hours. TNF-α levels were measured from cell-free supernatants by sandwich ELISA (BioSource #CHC1751).

LPS stimulation of whole blood

Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson), and 500 µl of blood aliquoted into each well of a 24-well tissue culture treated plate. After the addition of inhibitor cells were stimulated with an optimal dose of LPS (*E. coli* strain B5:055, Sigma, at a final concentration of 1 $\mu g ml^{-1}$) and incubated at 37°C without CO_2 for 18 hours. TNF-α levels were measured from cell-free supernatants by sandwich ELISA (BioSource #CHC1751).

Rat LPS-induced TNF release

Male Lewis rats (180-200 g) are anaesthetised with Isofluor and injected i.v. with LPS* in a volume of 0.5 ml sterile saline. After 90 minutes blood is collected into EDTA tubes for preparation of plasma samples. Plasma is stored at -70°C prior to assay for TNF-α by commercial ELISA.

Rat CIA

Female Lewis rats (180-200 g) are anaesthetised with Isofluor and immunised i.d. at the base of the tail with 2 x 100 µl of emulsion containing 4 mg/ml bovine collagen II in 0.01 M acetic acid and Freund's Incomplete Adjuvant at a ratio of 1:1. A polyarthritis develops with onset from about 13 days post-sensitisation. The disease is mainly confined to the ankles and is quantified by plethysmometry. Results are expressed as change in paw volume over time.

Conclusion

In the p38 inhibitor assays described above, the compounds of the Examples have IC_{50} values of around 2 µM and below. The compounds of the invention are clearly potent inhibitors of p38 kinase, especially p38α kinase.

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